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PATHOLOGY AND PHYSIOLOGY OF STRUMA OVARII

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THYROID tissue develops fairly frequently in ovarian dermoids (table 1), although it is usually no more than a microscopic portion of the tumor. There is, however, a rare type of ovarian tumor, known as struma ovarii, in which thyroid tissue is a major constituent.[1] Some of these ovarian goiters are obvious teratomas, containing besides thyroid such tissues as skin, teeth, brain and intestinal epithelium. Others consist entirely of thyroid or of thyroid in association with a cystoma.

Boettlin in 1889 was the first to note the presence of thyroid tissue in an ovarian dermoid. Wilms, Merttens and Kroemer published reports

TABLE 1.—*Incidence of Thyroid Tissue in Ovarian Teratomas*

Author	Teratomas	Thyroid	Per Cent
Pick	21	6	28.6
Neumann	74	5	6.7
Rohdenburg	61	9	16.4
Mayer	131	2	1.5
Koucky	128	19	14.8
Meigs	27	2	7.4
Spencer	66	1	1.5
Tribedi and De	31	3	9.7
Gusberg and Danforth	297	8	2.7
Blackwell and associates	100	13	13.0
Saller	37	3	8.1
Total	973	71	Average 7.3

of similar cases. Then Gottschalk in 1899 described an ovarian tumor composed entirely of thyroid-like tissue. Thyroid tissue in the midst of a dermoid was not remarkable, but an ovarian tumor composed entirely of thyroid seemed improbable. Gottschalk concluded, despite its structural similarity to thyroid, that the tumor was derived from ovarian follicles. Because one portion had the histologic appearance of a malignant growth, Gottschalk named the tumor "folliculoma malignum."

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1. The term struma ovarii is often loosely applied to any ovarian teratoma containing thyroid tissue; only the tumors in which there has been considerable unilateral development of thyroid tissue should be so designated.

TABLE 2.—*Published Cases of Struma Ovarii*

Author	Year	Case	Age, Yr.	Pathology	Comment	No.
Adolf	1918	1	51	Dermoid with thyroid	Ascites	1
		2	40	Dermoid with thyroid	Dermoid of opposite ovary	2
Aisenstadt	1913	1	26	Dermoid with thyroid	Cystic ovary on opposite side	3
Anspach	1903	1	36	Dermoid with thyroid	.....	4
Aschkanasy	1936	1	36	Cystoma with thyroid	.....	5
		2	34	Cystoma with thyroid	Goiter present	6
		3	32	Dermoid with thyroid	.....	7
Moraes Barros, de Godoy and Delascio	1944	1	39	Thyroid	.....	8
Bauer	1914	1	27	Cystoma with thyroid	.....	9
Bell	1905	1	32	Cystoma with thyroid	.....	10
		2	52	Dermoid with thyroid	Goiter present	11
Boettlin	1889	1	28	Dermoid with thyroid	.....	12
Bolt	1923	1	61	Dermoid with thyroid	Ascites	13
Boxer	1911	1	42?	Thyroid	Ascites	14
		2	42?	Cystoma with thyroid	.....	15
		3	?	Thyroid	Dermoid of opposite ovary	16
Brandenburg	1936	1	38	Dermoid with thyroid	Goiter present	17
Brown	1942	1	57	Thyroid	Ascites	18
Bua	1922	1	24	Thyroid	Goiter present	19
Büll	1919	1	32	Cystoma with thyroid	.....	20
Cantor and Kogut	1936	1	21	Thyroid	Coincident pregnancy	21
Castano	1939	1	54	Dermoid with thyroid	Goiter present	22
Cleland	1910	1	?	Dermoid with thyroid	.....	23
Cohn and Kushner	1944	1	52	Dermoid with thyroid	.....	24
Dingels	1912	1	58	Cystoma with thyroid	Ascites	25
Eerland	1936	1	60	Thyroid	Cranial metastases	26
Emge	1940	1	31	Dermoid with thyroid	.....	27
		2	20	Cystoma with thyroid	Omental implants	28
Eversmann	1905	1	33	Cystoma with thyroid	.....	29
Fahmy	1936	1	64	Cystoma with thyroid	Ascites	30
Fiebach	1911	1	50	Cystoma with thyroid	Cyst of opposite ovary; ascites	31
Frank	1909	1	22	Dermoid with thyroid	.....	32
Frankel and Lederer	1928	1	50	Cystoma with thyroid	.....	33
		2	54	Dermoid with thyroid	Ascites	34
		3	34	Dermoid with thyroid	.....	35
Frankl	1912	1	42	Thyroid	Histologic evidence of malignancy	36
Frankl	1924	1	20	Dermoid with thyroid	.....	37
		2	23	Dermoid with thyroid	Cystoma of opposite ovary	38
Frankl	1931	1	62	Thyroid and Brenner tumor	Granulosa cell tumor of opposite ovary	39
Frankl	1934	1	30	Dermoid with thyroid	Goiter removed at age 18 yr.	40
Funke	1900	3	?	Dermoid with thyroid	.....	41
Gargano	1928	1	45	Thyroid with chorionepithelioma	Omental implants	42
Gemmell	1911	1	?	Dermoid with thyroid	.....	43
Giannettasio	1914	1	32	Teratoma with thyroid	Bilateral tumors; ascites	44
Glockner	1903	1	57	Dermoid with thyroid	.....	45
Gottschalk	1899	1	48	Thyroid	Ascites	46
Gusberg and Danforth	1944	1	53	Dermoid with thyroid	Goiter present	47
Haggag	1927	1	57	Cystoma with thyroid	.....	48
Heinsen	1932	1	74	Cystoma with thyroid, cartilage and bone	Goiter present	49
Hundley	1940	1	41	Dermoid with thyroid	.....	50

TABLE 2.—*Published Cases of Struma Ovarii—Continued*

Author	Year	Case	Age, Yr.	Pathology	Comment	No.
Kafka	1921	1	63	Dermoid with thyroid	Ascites	51
		2	22	Dermoid with thyroid	.....	52
		3	60	Dermoid with thyroid	.....	53
Katsurada	1901	4	48	Dermoid with thyroid	.....	54
King and Norris	1930	1	45	Cystoma with thyroid	.....	55
		2	36	Dermoid with thyroid	Coincident pregnancy	56
		3	43	Dermoid with thyroid	.....	57
Kleine	1934	1	39	Cystoma with thyroid	.....	58
		2	55	Dermoid with thyroid	Goiter present	59
		3	58	Cystoma with thyroid	Ascites	60
		4	49	Teratoma with thyroid	.....	61
		5	38	Teratoma with thyroid	Goiter present	62
		6	35	Teratoma with thyroid	.....	63
Koerner	1925	1	26	Dermoid with thyroid	.....	64
Kovacs	1924	1	33	Thyroid	Goiter present	65
Kretschmar	1901 1902	1	48	Cystoma with thyroid and bone	Goiter present; patient died 2 yr. later of "Rezidiv"; ascites	66
Kroemer	1899	10	?	Dermoid with thyroid	.....	67
Lanz	1902	1	54	Thyroid	Cirrhosis of the liver and ascites present	68
Lecene	1904	1	40	Dermoid with thyroid	.....	69
		2	?	Dermoid with thyroid	.....	70
Lindquist and Forselius	1915	1	52	Dermoid with thyroid	.....	71
Lochrane	1933	1	43	Cystoma with thyroid	.....	72
Lyday	1934	1	19	Cystoma with thyroid	.....	73
Macleod	1932	1	?	Dermoid with thyroid	Dermoid of opposite ovary	74
		2	?	Dermoid with thyroid	.....	75
Manasse	1926	1	53	Teratoma with thyroid	Bilateral teratomas with thyroid; papillary tumor of thyroid tissue	76
Masson and Mueller	1933	1	49	Cystoma with thyroid	Goiter; ascites	77
		2	55	Cystoma with thyroid	Ascites	78
		3	63	Thyroid with calcification	.....	79
		4	39	Cystoma with thyroid	Goiter; ascites	80
		5	38	Thyroid	Nodule of thyroid tissue in ovary only 6 mm. in diameter; goiter also present	81
		6	43	Cystoma with thyroid	Goiter present	82
Maxwell	1911	1	47	Cystoma with thyroid	.....	83
Merttens	1897	1	6	Dermoid with thyroid	.....	84
Meyer	1903	1	55	Thyroid with bone	Ascites	85
Moench	1915	1	44	Dermoid with thyroid	Goiter present	86
	1929	2	46	Dermoid with thyroid	Goiter present; opposite ovary cystic	87
		3	49	Dermoid with thyroid	Thyrotoxicosis?	88
Mohr	1912	1	62	Dermoid with thyroid	Metastasis to liver and diaphragm	89
Möller	1915	1	35	Dermoid with thyroid	.....	90
Momigliano	1924	1	34	Dermoid with thyroid	.....	91
Morgen	1924	2	55	Dermoid with thyroid; bilateral	Peritoneal implantations, which underwent spontaneous regression; ascites	92
Murray, Dockerty and Pemberton	1942	1	56	Dermoid with thyroid	Granulosa cell tumor of opposite ovary	93
Neu (same case reported by Sitzler in 1913)	1911	1	42	Thyroid	.....	94

TABLE 2.—*Published Cases of Struma Ovarii—Continued*

Author	Year	Case	Age, Yr.	Pathology	Comment	No.
Neumann	1937	1	28	Dermoid with thyroid	.....	95
		2	30	Cystoma with thyroid	Cartilage and bone present	96
		3	27	Cystoma with thyroid	Goiter present	97
Nicholson	1937	1	39	Cystoma with thyroid	.....	98
Norris	1909	1	51	Dermoid with thyroid	.....	99
Outerbridge	1913	1	37	Cystoma with thyroid	Ascites	100
		2	52	Dermoid with thyroid	.....	101
Parodi	1922	1	53	Cystoma with thyroid	Ascites	102
Pick	1902	1	33	Dermoid with thyroid	.....	103
Piltz	1910	1	57	Dermoid with thyroid	.....	104
Plauchu and Gaudon	1923	2	21	Dermoid with thyroid	.....	105
Plaut	{1931 {1933	1	47	Cystoma with thyroid	Histologically "malignant" areas	106
		2	35	Cystoma with thyroid	Cystoma of opposite ovary	107
		3	55	Cystoma with thyroid	Ascites	108
Polano	1904	1	56	Thyroid	Ascites	109
Poli	1910	1	41	Dermoid with thyroid	.....	110
Pollosson and Violet	1905	1	63	Dermoid with thyroid	.....	111
Proescher and Roddy	1910	1	36	Cystoma with thyroid	.....	112
		2	26	Cystoma with thyroid	Bone also present	113
		3	37	Thyroid	Metastasis to liver, omentum and mesentery	114
Ribbert	1905	1	?	Thyroid in "tumor" of ovary	.....	115
Riebel and Riebel	1927	1	33	Thyroid	.....	116
Ries	1914	1	?	Cystoma with thyroid	.....	117
Rothe	1904	2	27	Dermoid with thyroid	Dermoid of opposite ovary	118
Ruiz	1927	1	45	Dermoid with thyroid	.....	119
Sailer	1943	1	46	Thyroid	Bilateral dermoids previously removed	120
		2	64	Thyroid	Ascites	121
Saidl	1937	1	36	Dermoid with thyroid	Goiter present	122
Sanders	1935	1	51	Cystoma with thyroid	Goiter present	123
Schauta	1911	1	43	Cystoma (?) with thyroid	.....	124
Schickele	1911	1	29	Cystoma with thyroid	.....	125
Schipper	1907	1	51	Thyroid	.....	126
Shapiro	1930	1	38	Thyroid	Metastasis to peritoneum and omentum; goiter present	127
Shaw, E. H	1926	1	71	Dermoid with thyroid	.....	128
Shaw, W	1932	1	34	Cystoma (?) with thyroid	.....	129
Swanton	1906	1	42	Cystoma with thyroid	.....	130
Thaler	1923	1	40	Cystoma with thyroid	Dermoid of opposite ovary; ascites	131
Trapl	1935	1	29	Dermoid with thyroid	.....	132
		2	43	Cystoma with thyroid and endometrioma	.....	133
Trettenero	1931	1	49	Dermoid with thyroid; pure thyroid tumor of opposite ovary	.....	134
Tribedi and De	1944	1	25	Dermoid with thyroid	.....	135
		2	50	Dermoid with thyroid	.....	136
		3	38	Bilateral dermoids with thyroid	.....	137
Ulesko-Stroganown	1905	1	54	Bilateral pure thyroid tumors	.....	138
Vagedes	1904	1	26	Cystoma with thyroid	.....	139
Walthard	1908	1	55	Dermoid with thyroid	Goiter present	140
		2	33	Dermoid with thyroid	.....	141
		3	?	Cystoma with thyroid	Goiter present	142

TABLE 2.—*Published Cases of Struma Ovarii—Continued*

Author	Year	Case	Age, Yr.	Pathology	Comment	No.
Werth	1928	1	36	Thyroid with bone and calcification	Implantation of tumor on pelvic peritoneum; ascites	143
Wilms	1895	18	24	Dermoid with thyroid	Dermoid of opposite ovary at 18 yr.	144
		19	52	Dermoid with thyroid		145
	1896	1	22	Teratoma with thyroid		146
Witherspoon	1932	1	35	Dermoid with thyroid	Dermoid of opposite ovary	147
Wood	1909	1	?	Cystoma with thyroid and bone		148
		2	?	Cystoma with thyroid		149
		3	40	Cystoma with thyroid	Histologically "malignant" areas	150
		4	?	Dermoid with thyroid		151
Wynne, McCartney and McClendon	1940	1	26	Thyroid	Metastasis to ischium	152
Present case	....	1	58	Thyroid	Adhesions present; tumor thrombi in veins of tumor; goiter present	153

Kretschmar in 1901 reported a cystoma of the ovary containing tissue similar to that described by Gottschalk. Kretschmar was impressed by the intimate relation of the follicles to the lymphatic vessels and at first regarded the tumor as an endothelioma. In a later paper (1904) he identified it as thyroid tissue, which he believed had metastasized to the ovary from the thyroid gland.

In 1902 Pick presented a case of ovarian dermoid containing thyroid and stated that of twenty-one dermoids studied six contained thyroid tissue. He concluded that all ovarian tumors containing thyroid must be teratomatous in origin and assigned them the name "teratoma strumoides thyroideale ovarii." Pick cited the cases of Gottschalk and Kretschmar as examples in which thyroid tissue had developed while all other teratomatous elements were suppressed.

Since this time, only Bauer has seriously questioned the identity of the thyroid tissue. Bauer attempted to show that these tumors are a form of cystadenoma in which a thyroid-like structure is produced by downgrowth of the surface epithelium of the ovary. While this may be the correct interpretation of the particular case described by Bauer, such an explanation does not hold for struma ovarii in general. Nicholson has shown that although many of the published reports of cases are lacking in the detail necessary to a scientific demonstration there is, nevertheless, an abundance of proof that these tumors are composed of genuine thyroid tissue.

It is the purpose of this paper to describe the pathologic changes and functional activity of thyroid tissue in ovarian tumors. This study is based on investigation of a case of struma ovarii and analysis of 152 previously published reports of cases (table 2). While a few reports of cases were inaccessible and no doubt a few were overlooked, it is believed that the total number of published cases cannot be much in excess of 160.

REPORT OF A CASE

Clinical Record.—Mrs. S. C., a 58 year old white housewife was examined Feb. 10, 1940. She had borne ten children, seven alive and three stillborn, and had ceased to menstruate at 49 years of age. Her mother died of cancer of the stomach, and one sister had goiter. Her complaint was of pelvic discomfort, a sense of pressure on the bladder and extreme urinary frequency. Two and one-half years before, her physician had noted the presence of a small nodular goiter associated with loss of weight, nervousness, tachycardia (rate 110) and basal metabolic rate of + 19 per cent.

Physical examination showed that her height was 59½ inches (151 cm.), weight 120 pounds (54.4 Kg.), temperature 98.2 F., pulse rate 100; respiratory rate 22 and blood pressure 140 systolic and 80 diastolic. There was no lid lag or exophthalmos. The right lobe of the thyroid was palpable and contained a firm nodule 2 cm. in diameter; the left lobe was barely palpable. On pelvic examination a round hard mass about 5 cm. in diameter could be felt in the left adnexa. A roentgenogram of the chest showed slight ventricular hypertrophy on the left side, a slightly widened aortic arch and some increase in hilar and bronchovascular markings.

Laboratory examination showed a hemoglobin content of 13.3 Gm., erythrocytes 5,000,000 and leukocytes 7,800; the differential count was neutrophils 60 per cent, eosinophils 2 per cent, lymphocytes 32 per cent and monocytes 6 per cent; the sedimentation rate was 26 mm. in one hour (Westergren). Serum reactions to Kahn and Kline tests were negative. Examination of urine gave these findings: acid, quantity not sufficient; albumin, 1 plus, and no sugar. Microscopically there were leukocytes 2 plus and fine granular and hyaline casts 3 plus.

Operation was performed Feb. 27, 1940, with the patient under ether anesthesia. The pelvic organs were exposed through an incision in the lower midline of the abdomen. The greater omentum was found to be densely adherent to the parietal peritoneum; there was no ascites. There was a solid tumor of the left ovary, 5 cm. in diameter, which was well encapsulated and not adherent to any other viscera, except to the fimbriae of the left tube. The right ovary was small and atrophic and appeared normal. There were no signs of peritoneal implantations or metastases. Palpation of organs of the upper part of the abdomen was impossible because of the dense omental adhesions. Bilateral salpingo-oophorectomy and appendectomy were done, and the wound was closed in layers. Convalescence was uneventful, and the patient is alive and well six years later.

Pathologic Examination.—The tumor measured 5 by 3 by 4 cm., weighed 45 Gm. and was covered by a dense capsule, which was adherent to the fimbriae of the tube. On section, the tumor was solid, grayish white and of firm consistency. There was a fine trabeculated appearance, with small translucent areas 1 or 2 mm. in diameter between the septums. The remnants of ovarian tissue were visible at one pole and contained several small thin-walled cysts 2 or 3 mm. in diameter.

The tissue was fixed in 5 per cent solution of formaldehyde and embedded in paraffin, and a large number of representative sections were cut. These were stained with hematoxylin and eosin, Kraus's polychrome methylene blue tannic acid colloid stain and mucicarmine.

Microscopically, the tumor consisted of remnants of ovary, differentiated thyroid tissue, thyroid adenoma and small foci of osseous formation. The remnant

of ovary was no more than a thin shell of atrophic ovarian tissue lying on one pole of the thyroid tumor. There were no ovarian follicles; an old corpus albicans was present.

The well differentiated portion of the tumor consisted of follicles filled with homogeneous acid-staining colloid, which exhibited the vacuolization and retraction

Fig. 1.—Junction of ovarian and thyroid tissue. Note the old corpus albicans. Hematoxylin and eosin; × 92.

characteristic of thyroid colloid. This colloid stained blue and violet by Kraus's method but was nowhere fuchsinophilic. No mucin or pseudomucin was demonstrable in any part of the tumor by mucicarmine. The follicular epithelium was low columnar in the small follicles, cuboid in the medium-sized follicles and flattened in the large follicles. The diameter of the follicles was determined by actual

measurement of 1,200 vesicles and found to average 70 microns. The stroma was fairly abundant, with numerous fibrous septums producing lobulation. The tissues were well supplied with many small thin-walled blood vessels. Several follicles were observed to be filled with large, foamy phagocytic cells.

The undifferentiated tissue was distributed throughout the tumor, occurring in masses and nodules varying from microscopic size to 8 or 10 mm. in diameter. The

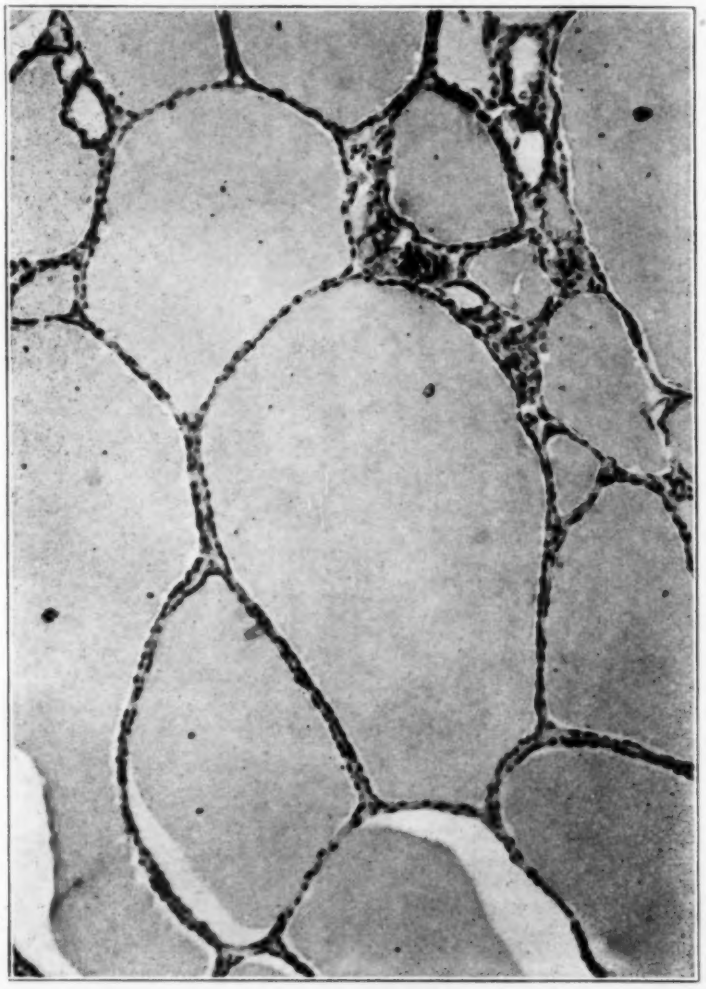

Fig. 2.—Thyroid tissue, area of distinct colloid storage, large follicles and flattened epithelial cells. Hematoxylin and eosin; × 137.

cells which made up these masses were closely packed and usually arranged in cords and columns separated from one another by a delicate stroma. In a few places the cells showed a tendency to arrange themselves in a circular fashion and thus form primitive follicles, which in some instances contained a droplet of

colloid. The cells were fairly uniform in size and staining qualities and closely resembled the cuboid cells of the medium-sized follicles. Mitotic figures were rare. These adenomatous areas were actively growing, with rounded borders compressing the adjacent follicles and blending imperceptibly with the interfollicular cells of the more highly differentiated thyroid tissue.

Fig. 3.—Solid area of tumor showing striking epithelial proliferation without colloid storage. Hematoxylin and eosin; × 153.

An intermediate grade of differentiation was exhibited in some places where the follicles were irregular in size and shape and contained little colloid. The epithelial cells of these follicles were loose, seemed to fall away frequently from their neighboring cells and by proliferation filled the lumen of many follicles.

Malignant tendencies were indicated by this disorder, by the active proliferation of the adenomatous tissue, by the invasion of the fibrous capsule by epithelial cells

and especially by the invasion of blood vessels by the tumor cells. Numerous instances were noted in which small and medium-sized veins contained thrombi made up in large part of tumor cells, sometimes arranged in follicles containing colloid.

Several foci of osseous formation were present in the tumor, all being of microscopic size. One deposit of calcium was seen. No other tissue was found.

The right ovary showed senile atrophy; the tubes and appendix were normal.

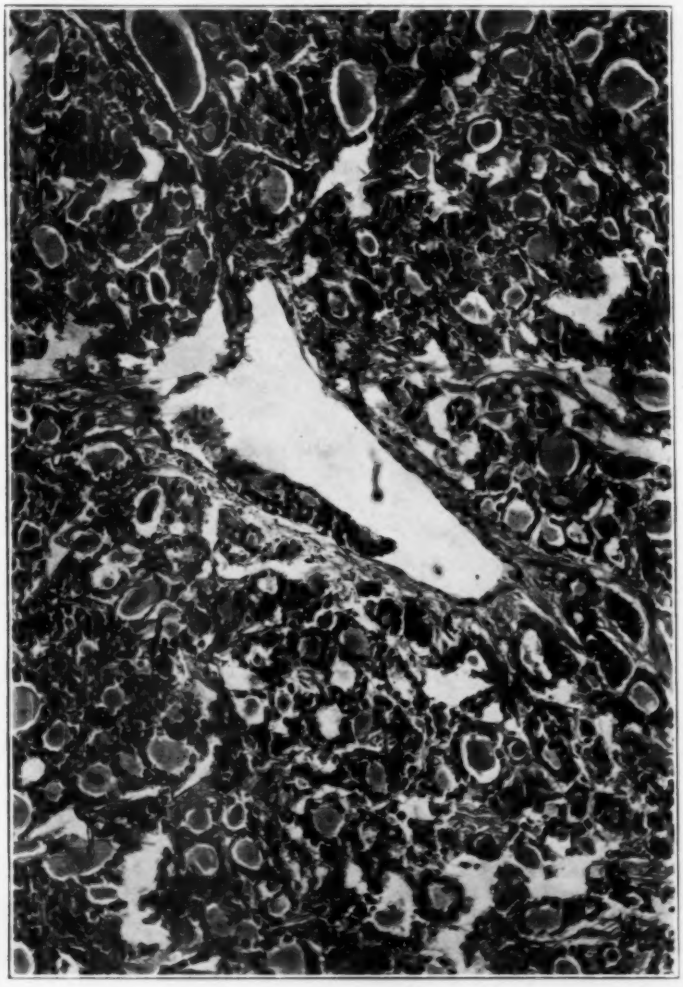

Fig. 4.—Invasion of a large vein by tumor tissue; small follicles predominate in this area, and interfollicular cells are numerous. Hematoxylin and eosin; × 153.

Metabolic Studies.—The patient's basal metabolic rate was not determined during the immediate preoperative period. A test made two and one-half years previously (June 4, 1937) had shown a rate of + 19 per cent. After the histologic character of the tumor had been ascertained, tests were made with results as

follows: June 29, 1940, + 36 per cent and Oct. 24, 1940, + 12 per cent. During this time there was a gain in weight from 118 to 124 pounds (53.5 to 56.2 Kg.).

Determination of the patient's blood iodine content was carried out Oct. 24, 1940, by the method of Davison, Zollinger and Curtis. This test showed the acetone-soluble fraction to be 5.42 micrograms per hundred cubic centimeters of whole blood, water-soluble fraction 0.16 micrograms per hundred cubic centimeters and insoluble fraction 1.18 micrograms per hundred cubic centimeters.

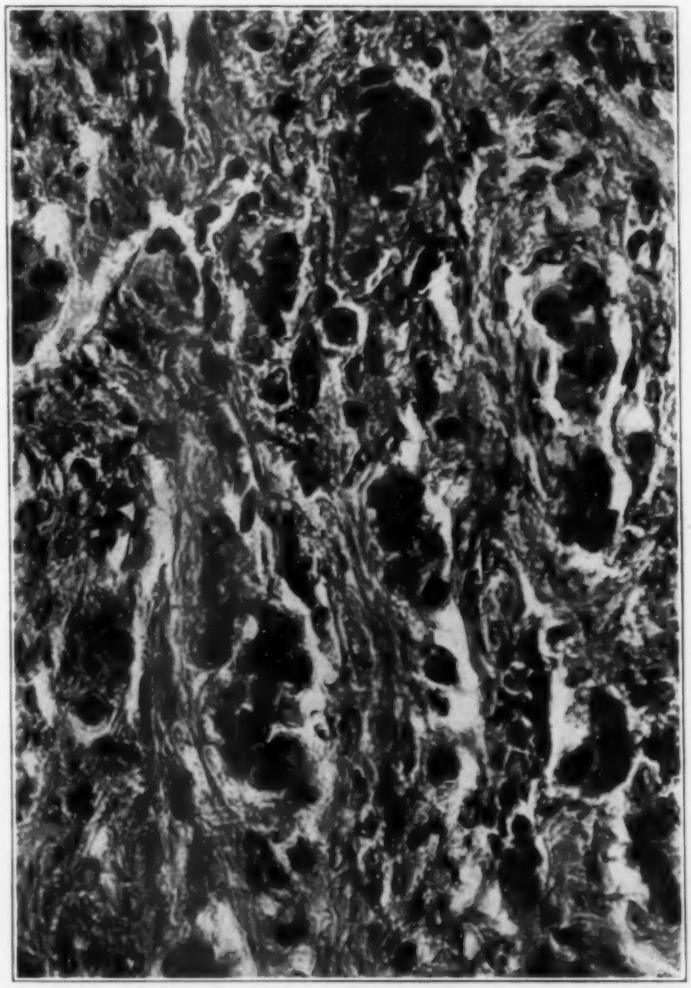

Fig. 5.—Invasion of the narrow fibrous capsule of the tumor by a cluster of epithelial cells. Hematoxylin and eosin; × 369.

The estimation of the iodine content of the tumor was performed by the method of Matthews, Curtis and Brode. Eight blocks of tissue were cut from representative portions of the tumor for analysis. The concentration of iodine per hundred grams of tumor tissue (wet weight) varied in these blocks from 1.279 to 5.480 mg. and averaged 2.376 mg.

PATHOLOGY

1. *Incidence and Types of Tumors.*—Ovarian tumors containing thyroid tissue occur at all ages. Merttens reported the case of a 6 year old girl and Heinsen that of a woman of 74. The average age in 139 cases was 42 years.

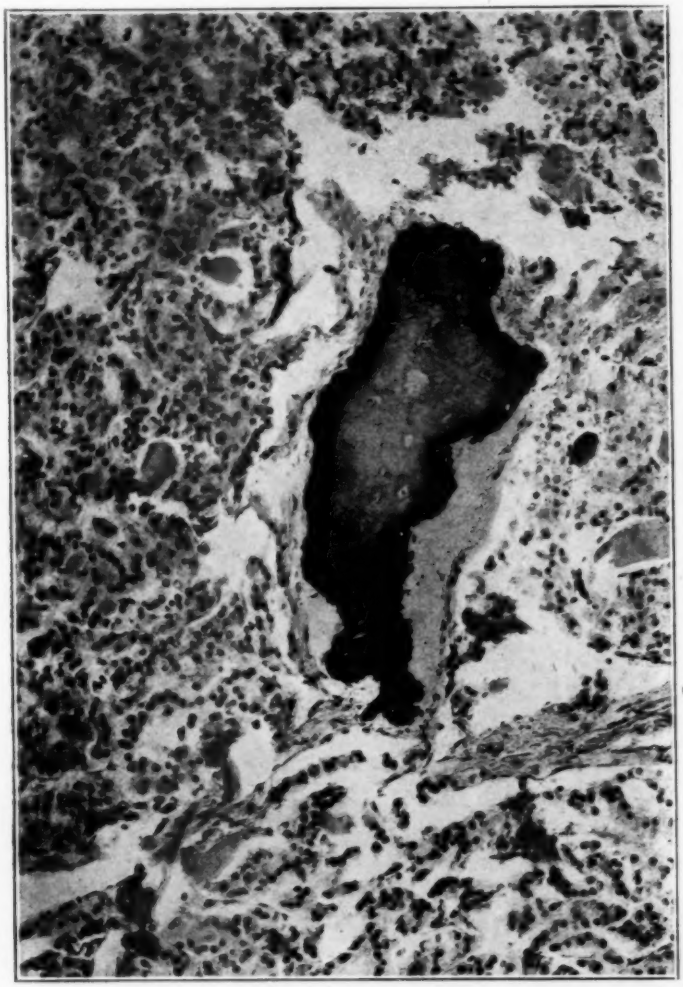

Fig. 6.—Focus of osseous formation in the tumor. Hematoxylin and eosin; × 153.

Thyroid tissue occurs in several varieties of ovarian tumor. If the case of Ribbert, who gives no information whatever, is excluded, there are 152 cases, including my own, in which some statement is made concerning the type of tumor present (table 3).

Dermoids constitute the largest group of tumors which exhibit thyroid tissue. Seventy-six of the tabulated cases fall in this group. In some of the cases the author has given a clear objective description which leaves no doubt that he was dealing with a dermoid or teratoma composed of multiple tissues. In other cases there is only the author's statement that the tumor was a dermoid or teratoma. Many of the dermoids were associated with a cystoma of the serous or pseudomucinous variety.

In 47 cases a serous or pseudomucinous cyst has been described in combination with a solid tumor consisting of thyroid tissue without other recognizable teratomatous elements. Tumors have been included in this group even though bone or cartilage has been found, for the reason that these tissues may arise anywhere in the body and are not necessarily characteristic of teratomas.

Thyroid tumors occurring alone, without cystoma and without other teratomatous elements (but not excepting bone or cartilage),

TABLE 3.—*Varieties of Struma Ovarii*

Pathologic Conditions	Cases	Per Cent
Dermoid with thyroid	76	50
Cystoma with thyroid	47	31
"Pure" thyroid	26	17
Miscellaneous	3	2

are listed twenty-six times in the series. These are the cases of so-called pure struma ovarii; the present specimen falls into this classification. The smallest tumor of this sort was a 6 mm. nodule of thyroid tissue found by Masson and Mueller at autopsy of a 38 year old woman who died of thyrotoxicosis and hepatic atrophy. Some of these tumors have reached considerable size, tumors the "size of a child's head" having been reported by Gottschalk (1899) and Ulesko-Stroganowa.

There remain 3 special cases which cannot be classified with any of the preceding groups. Frankl (1931 and 1934) described a thyroid tumor with a Brenner tumor of the same ovary and a granulosa cell tumor of the opposite ovary. Gargano described a tumor weighing 1.5 Kg. removed from a 45 year old woman; the tumor consisted mostly of thyroid, but in some areas epithelial syncytia were present which were typical of chorionic carcinoma. The patient exhibited many tumor implants over the omentum and died five months after the operation. Finally, in Trapl's second case the growth consisted of a cystoma with thyroid tissue and an endometrial inclusion.

2. Tumors of the Opposite Ovary.—A tumor of the opposite ovary has been reported in 21 cases of struma ovarii. Thyroid tissue was

present bilaterally in 6 cases, or approximately 4 per cent of the series. The pathologic types of bilateral tumors which have been described are recorded in table 4.

3. Ascites and Adhesions.—Ascitic fluid was found in 26 cases, or 17 per cent, and adhesions are mentioned five times in the literature. My own patient did not have ascites, but adhesions were conspicuous. These findings cannot be considered indicative of malignant growth, as they are frequently found with other benign ovarian tumors. Thus, Cabot found ascites in 7.9 per cent of ovarian cystomas; though this frequent association of benign ovarian tumors with ascites is well known, its cause is not yet understood.

TABLE 4.—*Thyroid Tissue in Association with Bilateral Ovarian Tumors*

	Author	Type of Principal Tumor	Tumor of Opposite Ovary
1.	Plaut	Cystoma with thyroid	Cystoma
2.	Fiebach	Cystoma with thyroid	Cystoma
3.	Thaler	Cystoma with thyroid	Dermoid
4.	Ulesko-Stroganowa	Thyroid	Thyroid
5.	Boxer	Thyroid	Dermoid
6.	Sailer	Thyroid	Dermoid
7.	Moench	Dermoid with thyroid	Cystoma
8.	Aisenstadt	Dermoid with thyroid	Cystoma
9.	Frankl (1924)	Dermoid with thyroid	Cystoma
10.	Murray and associates	Dermoid with thyroid	Granulosa cell tumor
11.	Manasse	Dermoid with thyroid	Dermoid with thyroid
12.	Morgen	Dermoid with thyroid	Dermoid with thyroid
13.	Giannettasio	Dermoid with thyroid	Dermoid with thyroid
14.	Tribedi and De	Dermoid with thyroid	Dermoid with thyroid
15.	Rothe	Dermoid with thyroid	Dermoid
16.	Adolf	Dermoid with thyroid	Dermoid
17.	Witherspoon	Dermoid with thyroid	Dermoid
18.	Macleod	Dermoid with thyroid	Dermoid
19.	Wilms (1895)	Dermoid with thyroid	Dermoid
20.	Trettenero	Dermoid with thyroid	Thyroid
21.	Frankl (1931)	Thyroid with Brenner tumor	Granulosa cell tumor

4. Metastasis.—Dissemination of these tumors has occurred in a few instances.[2] Three distinct types of metastasis have been found: local implants on the peritoneum and omentum (Morgen, Shapiro, Werth and Emge), regional spread, with nodules in the liver (Proescher and Roddy [third case] and Mohr), and distant metastasis to bone via the blood stream (Eerland and Wynne, McCartney and McClendon). The local implants may be benign and not incompatible with a long survival period (Morgen's patient lived eighteen and one-half years). Proescher and Roddy's patient with metastasis to the liver showed recurrence in five months and died in one year; Mohr's patient died on the fifteenth postoperative day. Skeletal metastasis may be highly

2. It is to be noted that Ulesko-Stroganowa's case of "metastasis" of pure struma from one ovary to the other is not included. It is apparent from my tabulation that bilateral teratomas are not rare, and without other evidence of metastasis such an explanation is extremely unlikely.

malignant, as in Eerland's case, or relatively benign, as in the case of Wynne and associates, in which a metastasis to the ischium was removed surgically and no recurrence had been noted within six months.

Gargano has reported the surgical removal of a 1,500 Gm. tumor from a 45 year old woman; there were numerous nodules in the omentum, and the patient died five months after operation; autopsy was not performed. Microscopic examination of the tumor showed it to be composed principally of thyroid, which was combined with a chorionic carcinoma. It is not clear whether the malignity is to be attributed entirely to the chorionic carcinoma or whether there was also dissemination of the thyroid tissue.

5. Coincidence of Cervical Goiter and Struma Ovarii.—Cervical goiter has been recorded twenty-five times in the entire series of 153 cases, an incidence of 16.3 per cent. Since many of the reports of cases in the literature do not provide a complete clinical description of the patient, the true incidence of goiter with struma ovarii is probably higher.

6. The Cellular Pathology of the Thyroid Tissue in Struma Ovarii.—The usual histologic changes of struma ovarii appear to have been well illustrated in my own case. Point by point, the tissue is identical with the structure of the thyroid gland. There are the same rounded follicles, lined with cubical or flattened epithelium. The colloid is homogeneous, tends to retract from the epithelium and is frequently vacuolated. The staining qualities are those of colloid, not mucin or pseudomucin. The stroma is delicate, and interfollicular cells are numerous. There is evidence of various levels of physiologic activity, with a few large cystic follicles filled with colloid and in other places a somewhat hyperplastic gland with many small follicles.

The parallel extends farther. The tumor exhibits not only the differentiated architecture of adult thyroid tissue but also the proliferation and disorganization of a malignant thyroid adenoma. The potentially malignant nature is clearly shown by the numerous vessels containing tumor cells. That metastasis did not occur prior to operation seems remarkable, and one can only presume that such cells as may have been transported by the blood stream did not find a suitable site or did not possess sufficient vitality to establish a metastatic focus.

A histologic appearance of malignant growth has been described repeatedly. Gottschalk (1899) described his specimen as similar to "struma maligna." Such reports must be examined in the light of modern knowledge of thyroid neoplasia. Histologic criteria of malignant growths of the thyroid are not so easily formulated as for most epithelial organs. This difficulty arises from the structure of the gland itself, which consists of epithelial follicles set directly on the

tissue and others on the basis of dry weight. The maximum values recorded are those of Emge, 1.018 mg. of iodine per gram of wet tissue, and of Masson and Mueller's first case, 1.05 mg. of iodine per gram of dry weight. These concentrations correspond to the iodine content of the normal adult thyroid gland. Most of the reports, however, show small quantities of iodine, indicating that iodine storage is minimal in the majority of these tumors. All the reports listed in table 5 show significant amounts of iodine except Plaut's second case, which is in the same range as the usual concentration of iodine in the ovary (30 to 160 micrograms per hundred grams).

2. Biologic Evidence of Physiologic Activity of Struma Ovarii.—Plaut studied the physiologic activity of these tumors by means of biologic tests. He investigated three tumors and found that the acetonitril reaction and the reaction to the tadpole test were positive in two tumors containing iodine; the reactions were negative in the third case, in which no iodine was found. Kleine found the Reid Hunt reaction positive in his sixth case but denied that the test was of an intensity characteristic of thyroid. Plaut's results indicate that in struma ovarii, as in the thyroid gland, the biologic activity parallels the iodine content.

3. Clinical Evidence of Physiologic Activity of Struma Ovarii.—Symptoms of thyrotoxicosis have been frequently cited as evidence of the physiologic activity of struma ovarii. In many cases the data are wholly inadequate and cannot be regarded as significant. In other cases there was an associated goiter present, which may have been partially or wholly responsible for the symptoms noted. Including my own, 17 patients have shown symptoms of thyrotoxicosis. Of these I should delete those of Moench (1929), Saidl and Aschkanasy for insufficient data. The symptoms in 2 cases (Kovacs, Cantor and Kogut) subsided before any operation was done. In 4 cases, including my own (Brandenburg and Masson and Mueller [cases 1 and 5]), there was a cervical goiter present, which could have accounted for the symptoms. Seven patients (Castano, Emge [cases 1 and 2], Hundley, Kleine [case 6], Neumann [case 3] and Gusberg and Danforth) seem to have shown significant alleviation of symptoms following operation. Masson and Mueller's second case cannot be interpreted as there was an elevated basal metabolic rate after operation but no goiter is mentioned. Neumann's case presents the interesting but puzzling observation that the struma colli diminished in size and the thyrotoxic symptoms abated after removal of the tumor. The published data are summarized in table 6.

It is worthy of comment that thyroid intoxication is dependent on more than an increase in the mass of thyroid tissue contained in the body. The functional activity of the thyroid gland is largely regu-

TABLE 6.—*Symptoms of Thyrotoxicosis Associated with Struma Ovarii*

Investigator	Case	Symptoms	Basal Metabolic Rate	Comment

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Investigator	Case	Symptoms	Basal Metabolic Rate	Comment
Aschkanasy	3	Sweats, palpitation and diarrhea	.....	
Brandenburg	1	Loss of weight, palpitation, dyspnea and tachycardia	+29.8	Symptoms not improved by removal of tumor, though basal metabolic rate fell temporarily to +6.6; thyroidectomy done, with relief
Cantor and Kogut	1	Tachycardia, sweats; exophthalmos present 3 yr. previously	.....	Patient 2 mo. pregnant at operation; normal delivery at term
Castano	1	Pulse rate 110	+36	Basal metabolic rate fell to +10 after operation
Emge	1	Tachycardia	+12 to +34	Basal metabolic rate fell to —14 after operation; symptoms relieved
	2	Tachycardia; loss of weight; exophthalmos	+6.3 to +16.5 postoperative	Removal of omental metastases resulted in relief of symptoms; basal metabolic rate +4
Hundley	1	Fine tremor	+22 and +42 before operation; +30 after subtotal thyroidectomy	Basal metabolic rate not reduced by subtotal thyroidectomy but fell to —6 after removal of tumor
Kleine	6	Thyrotoxic	.....	Serum Reid-Hunt reaction positive before operation and negative after removal of tumor
Kovacs	1	Exophthalmos; patient previously showed signs of thyrotoxicosis, but these subsided before operation	.....	
Masson and Mueller	1	Thyrotoxic	+15	Basal metabolic rate —4 after subtotal thyroidectomy and removal of tumor
	2	Thyrotoxic	No preoperative determination	Basal metabolic rate +32 and +30 postoperatively
	5	Severe thyrotoxicosis; patient died from thyrotoxicosis and atrophy of liver	+47 to +82	Parenchymatous goiter present; ovarian thyroid 6 mm. in diameter found at autopsy
Moench	3	Fine tremor, irregular action of heart	.....	Symptoms relieved by operation; no iodine found in tumor
Neumann	3	Thyrotoxic	+40	Blood iodine 35 micrograms per 100 cc. before operation; struma colli diminished in size; basal metabolic rate returned to normal and symptoms relieved after removal of tumor
Saidl	1	Tachycardia, tremor	.....	
Gusberg and Danforth	1	Palpitation, perspiration, nervousness, slight tremor and tachycardia	+30 to +60 before thyroidectomy; +10 after thyroidectomy; —14 after removal of struma ovarii	Large cervical goiter; blood iodine 15.1 micrograms per 100 cc. before operation; thyroidectomy performed; colloid goiter found
Author's case	1	Tachycardia, loss of weight and nervousness	+19 (determination made 2½ yr. prior to operation)	No apparent relief from removal of tumor; symptoms attributed to coexisting toxic nodular goiter; symptoms have gradually subsided

tissue and others on the basis of dry weight. The maximum values recorded are those of Emge, 1.018 mg. of iodine per gram of wet tissue, and of Masson and Mueller's first case, 1.05 mg. of iodine per gram of dry weight. These concentrations correspond to the iodine content of the normal adult thyroid gland. Most of the reports, however, show small quantities of iodine, indicating that iodine storage is minimal in the majority of these tumors. All the reports listed in table 5 show significant amounts of iodine except Plaut's second case, which is in the same range as the usual concentration of iodine in the ovary (30 to 160 micrograms per hundred grams).

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lated by extrathyroid factors. Presumably, the ovarian thyroid falls under the influence of these same regulatory factors; to what degree a tumor of this sort may function autonomously is not known.

THE ORIGIN AND NATURE OF STRUMA OVARII

The origin of thyroid tissue in ovarian tumors has been explained in various ways. It has been denied that the tissue is true thyroid. Gottschalk considered the tumor a "folliculoma" arising from ovarian follicles. Bauer was able to discern what he regarded as evidence of the origin of the tumor by invagination of the covering epithelium (mesothelium) of the ovary. Finding no iodine in the tumor, he concluded that it was a cystadenoma bearing a structural resemblance to thyroid and asserted his belief that every so-called struma ovarii was in reality a cystadenoma. In the light of the histologic studies and evidence of physiologic activity which I have cited, such a view is no longer tenable. Architecturally and physiologically, these tumors are composed of genuine thyroid tissue.

In approximately half of the cases of struma ovarii, the tumors exhibit other tissues obviously foreign to the ovary. These tumors belong to the general class of teratomas; those containing hair, sebaceous glands, sweat glands or teeth may properly be referred to as dermoids. In such tumors the thyroid is but one of several well differentiated tissues; the presence of thyroid is no more remarkable than the occurrence of digestive epithelium or brain tissue.

The ovarian tumors which contain only thyroid or thyroid with a cystoma are generally considered to be teratomas in which all other tissues have undergone regression. This explanation was first advanced by Pick. That a teratoma may undergo extensive reduction in its constituent tissues is shown by Saxer's case, in which a tooth was found in an otherwise normal ovary.

Plausible as this theory is, there is no objective evidence of this regression of tissues in struma ovarii. Teratomas differ from other tumors in the greater potencies of their cells of origin (I do not propose to argue here which cells give rise to teratomas). Growth having been initiated in those cells, differentiation and organization can proceed along various lines. It is no longer necessary to suppose that definitive entodermal cells must precede the development of thyroid tissue; experimental embryology has demonstrated that the primary germ layers are not specific for the tissues which they usually produce. A teratoma is in no sense a fetus and so need not contain multiple tissues developing from specific germ layers. Rather, it may consist, as in the case of pure struma ovarii, of cells organizing and developing into one tissue only. Whether this is due to a primarily unidirectional stimulus or to

suppression of all other cell potencies or to actual overgrowth, with extinction of cells initiating other tissues, is not known.

SUMMARY

1. The historical background of struma ovarii is briefly reviewed.

2. A case of "pure" thyroid tumor of the ovary is reported. The tumor was found to consist of thyroid tissue in various grades of differentiation, with malignant invasion of the blood vessels; several foci of osseous formation were observed. The iodine content of the tumor was 2.4 mg. per hundred grams of wet weight. There was evidence of a mild thyrotoxicosis which is attributed to the coexistence of a nodular goiter.

3. The literature has been reviewed and 152 reported cases tabulated.

4. The average age incidence of struma ovarii is 42 years.

5. Cervical goiter has been found associated with struma ovarii in 16.3 per cent of the cases.

6. Ascites and peritoneal adhesions are frequently associated with these tumors.

7. Tumors of the ovary containing thyroid are of three general varieties: dermoids with thyroid, 50 per cent; cystoma with thyroid, 31 per cent, and pure thyroid, 17 per cent. Thyroid tissue has also been observed in association with chorionic carcinoma of the ovary and with a Brenner tumor. Coexisting tumors of the opposite ovary are not infrequent; thyroid tissue has been found bilaterally in 6 instances.

8. Although the majority of these tumors are benign, dissemination has been observed in 8 instances (5.3 per cent). Metastasis may be local, by implantation, or distant, as to the liver or skeletal system.

9. Histologically, struma ovarii reproduces the architecture of the thyroid gland in its normal physiologic variations. Rarely it may exhibit evidence of malignant growth in the form of malignant adenoma, papillary tumor or general anaplasia.

10. Physiologic activity of these tumors is demonstrated by the presence of iodine in approximately half of the tumors investigated, by the presence of thyroid hormone, as determined by the tadpole test, and, in a few instances, by clinical symptoms of thyrotoxicosis, relieved by the removal of the tumor.

11. All tumors of the ovary containing thyroid tissue are now considered to be teratomatous in nature.

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SURGICAL TREATMENT OF NEOPLASTIC OBSTRUCTION OF THE EXTRAHEPATIC BILIARY TRACT

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LOS ANGELES

TUMORS obstructing the common and hepatic bile ducts include primary neoplasms of the ducts and of the ampulla and carcinoma of the pancreas secondarily involving the common duct. Benign adenomas, polyps and congenital cysts may involve the ducts; however, carcinoma is relatively more frequent, and of this group carcinoma of the ampulla of Vater is perhaps the commonest.[1] All these primary lesions are extremely rare. Kelznack found two instances in four thousand, five hundred and seventy-eight routine postmortem examinations, and McGlinn found five in nine thousand. Of twenty-two thousand operations on the biliary tract at the Mayo Clinic, only forty-one were for carcinoma of the bile ducts.[2] The lesion occurs more frequently among men, and in about half of the cases it is associated with stones in the gallbladder or in the bile ducts. Primary carcinoma most frequently occurs at the junction of the cystic and common ducts or at the division of the common duct into its right and left branches. Occasionally the lesion is localized distal to the cystic duct, in which case it may be excised. Even when the lesion is in this favorable location, resection seldom results in permanent cure, although the procedure is justified on the basis of relieving jaundice and prolonging life. Of the group of 41 patients operated on for carcinoma of the bile ducts, only 1 is still alive and well. In this patient the lesion was localized, and it was excised by W. J. Mayo in 1927.

Early carcinoma or benign papilloma of the ampulla of Vater is usually amenable to local transduodenal excision. Small papillary carcinomas of the ampulla are usually of a low degree of malignancy, producing symptoms early and metastasizing late. For this reason radical procedures, such as the Whipple operation, are not justified in these cases. Aside from these lesions of the ampulla, the picture

Read at the sectional meeting of the American College of Surgeons, April 18, 1946, at Los Angeles.

1. Cole, W. H., and Elman, R.: Textbook of General Surgery, New York, D. Appleton-Century Company, Inc., 1939, p. 598.

2. Walters, W., in Christopher, F.: Textbook of Surgery, Philadelphia, W. B. Saunders Company, 1936, pp. 1334 and 1338.

as a whole, from the standpoint of permanent cure, is discouraging. Clagett, Counseller and Waugh, in their report of biliary surgery for 1942, 1943 and 1944 at the Mayo Clinic, made the statement that primary malignant lesions of the biliary tract are not amenable to surgical treatment.[3] Since most carcinomas of the bile ducts are located at or proximal to the cystic duct and since prognosis is fatal in these cases, procedures used for benign stricture, such as vitallium tubes and transplantation of external biliary fistulas, are not practical.

Secondary involvement or compression of the distal common duct offers a more hopeful outlook since the advent of the Whipple type of procedure. The duodenum and the head of the pancreas are resected, and the relief of biliary obstruction is made by anastomosing the gallbladder or the common duct to a portion of the proximal part of the gastrointestinal tract. Possibilities in this field of surgery are still being explored, and they continue to offer promise. Dixon recently reported a case in which he removed the entire pancreas for an extensive carcinoma of this organ.[4] The patient was living fifteen months after operation. The resultant diabetes was controlled by insulin.

When these factors are considered, the scope of surgical procedure for neoplastic obstruction of the extrahepatic biliary tract is limited essentially to four procedures: 1. Resection of the common duct is done when the lesion is localized to a portion of the duct distal to the cystic duct. If end to end anastomosis is not possible, the proximal portion of the duct may be transplanted into the duodenum, jejunum or stomach. 2. Transduodenal resection of the ampulla of Vater is performed for small benign or malignant papillomas of the ampulla. 3. A Whipple type of procedure is used for carcinoma of the pancreas and the more extensive carcinomas of the ampulla and distal common duct. 4. A palliative bile-shunting operation is done for inoperable malignant growths involving the distal common duct primarily or secondarily.

Four cases are reported which illustrate the procedures used and recommended in each of these types of cases.

REPORT OF CASES

CASE 1.—A white woman aged 65 years was aware of jaundice only two and one-half weeks before her admission to the hospital, although she stated that she had considerable itching of the skin for an indefinite time. She also complained of tenderness under the rib margin on the right side. She stated that her stools had been clay colored for some time. She had lost 10 pounds (4.5 Kg.) in weight

3. Clagett, O. T.; Counseller, V. S., and Waugh, J. M.: Proc. Staff Meet., Mayo Clin. **21**:5-10, 1946.

4. Waugh, J. M.; Dixon, C. F.; Clagett, O. T.; Bollman, J. L.; Sprague, R. G., and Comfort, M. W.: Proc. Staff Meet., Mayo Clin. **21**:25-46, 1946.

during the past month. She complained of indigestion but at no time had suffered from colic.

Physical examination revealed a fairly well nourished elderly woman who was extremely jaundiced. A tender mass was palpated in the region of the gallbladder. The icterus index was 182 units, the van den Bergh reaction was directly positive, the prothrombin time was twenty-six seconds and the albumin-globulin ratio was reversed (albumin 3.3 Gm. and globulin 5.65 Gm. per hundred cubic centimeters). The urine contained bile but was otherwise normal. Other physical findings were irrelevant. The preoperative diagnosis was probable carcinoma of the head of the pancreas.

Operation was done on Jan. 28, 1944. A paris green type of liver was found, and the gallbladder was greatly enlarged and full of stones. A friable lesion of the common duct distal to the cystic duct was resected. Continuity of the common duct was reestablished by end to end anastomosis over the proximal portion of the T tube. The tube was inserted into the duct through an opening distal to the site of the anastomosis. A cholecystostomy was made, a dressed tube being used. The diagnosis according to the pathologic report on the section of the common duct removed was grade II adenocarcinoma of the bile duct (type B Duke).

When the patient was dismissed from the hospital, one month later, the stools were bile colored. Cholangiography showed diodrast passing into the duodenum. The hepatic ducts were not dilated, and the gallbladder was visualized. The icterus index was 31 units. Ten months later, symptoms recurred and the patient died. Postmortem examination revealed carcinoma completely obstructing both hepatic ducts.

Case 2.—A white woman aged 63 years complained of indigestion and painless jaundice for approximately one month. The jaundice steadily increased and was accompanied with pronounced pruritus. She stated that her stools were clay colored and that she had lost weight.

Physical examination showed a thin elderly woman who was deeply jaundiced. The liver was palpated 4 cm. below the costal margin, and an enlarged gallbladder was palpated. The prothrombin time was twenty-two seconds, the icterus index was 126 units and the van den Bergh reaction was directly positive. The albumin-globulin ratio was 1.1, with a normal total protein content. The preoperative diagnosis was obstruction of the common duct.

Operation was done on Feb. 29, 1944. The liver was enlarged, and grossly diffuse hepatitis was evident. No stones were palpated in the gallbladder, and exploration of the common duct did not reveal a stone. White bile drained from the common duct. The duodenum was opened, and a small papilloma of the ampulla of Vater was removed. A cautery resection of the ampulla, including the papilloma, was made, and the common duct was sutured to the duodenum. The opening in the duodenum was closed transversely, and a T tube was sutured in the common duct. According to the pathologic report the tumor was a benign papilloma of the ampulla of Vater.

On the fifth postoperative day the stools became light brown in color. The patient was dismissed from the hospital on the tenth postoperative day. The icterus index was 99.6 units. The report of the cholangiogram on dismissal revealed normal functioning of the extrahepatic biliary system. The referring physician reported that the patient died one year and eight months later. The postmortem diagnosis was cirrhosis of the liver, inflammatory obstruction of the

hepatic duct and carcinoma of the kidney. The jaundice subsided but never completely cleared up.

CASE 3.—A white man aged 39 years complained of painless jaundice, pruritus and epigastric distress for three months. He had lost 40 pounds (18.1 Kg.) in weight during this period. He stated that he had had some fever.

Physical examination revealed an emaciated, deeply jaundiced man. A tender mass was palpated in the upper part of the right side of the abdomen, which was believed to be the gallbladder. The sedimentation rate was 29 mm. in one hour, the urine contained bile and the icterus index was 145 units. Roentgenograms showed an indentation of the second and third portions of the duodenum. A diagnosis of carcinoma of the head of the pancreas was made.

Operation was performed on Sept. 20, 1945. An extensive carcinoma involving the distal part of the common duct and the head and body of the pancreas was found. Since there was no evidence of distant metastasis, a one stage modified Whipple operation was carried out. All but a small portion of the tail of the pancreas was removed. The patient was given 1,500 cc. of blood continuously during the operation, which lasted three and one-half hours.

The convalescence was essentially uneventful. On the fifth postoperative day the icterus index was 120 units, the serum amylase content 800 units and the blood sugar content 73 mg. On the fourteenth postoperative day the patient was entirely ambulatory, the stools contained bile despite an icterus index of 117 units and the serum amylase level had decreased to 400 units. In a follow-up letter from the patient's doctor three months following the operation, it was reported that the icterus index was 15.9 units and serum amylase content 267 units and that all routine laboratory data were normal. A second follow-up letter just received, six months postoperatively, reports that the patient is in good general health and has regained his lost weight and that 18 pounds (8.2 Kg.) of this loss of weight had been gained during the past two months. He has had occasional mild episodes of indigestion, which have subsided with the oral administration of pancreatin. His stools are reported to be normal in color, and he has had no jaundice. His serum amylase content is now 200 units, the blood sugar content 100 mg. and the icterus index 6 units.

CASE 4.—A white woman aged 48 years complained that during the four months prior to her admission to the hospital she had suffered from painless jaundice, pruritus, clay-colored stools and loss of weight.

Physical examination revealed a middle-aged, undernourished woman intensely jaundiced. A tender mass was palpated in the upper right quadrant which was consistent with an enlarged gallbladder. The icterus index was 90 units, and there was an immediate direct van den Bergh reaction in five seconds. A diagnosis of probable carcinoma of the head of the pancreas was made.

Operation was performed Sept. 14, 1939. An inoperable carcinoma which was primary in the head of the pancreas was found. A Rous type of cholecystojejunostomy was made. Convalescence was uneventful until the seventh postoperative day, when fulminating type III pneumonia developed, and the patient died within forty-eight hours.

COMMENT

Although the outlook for cure is not bright following surgical procedures for primary malignant growths of the common duct, such procedures may lengthen the life and enhance the comfort of the patient.

An occasional cure may be expected. In the case in which a localized carcinoma of the common duct was resected, the patient lived in comfort for ten months. From a technical standpoint it seems that the simplest and safest method of restoring continuity of the common duct is anastomosis over a T tube. This offers the advantage of subsequent removal of the tube and assurance that a foreign body is not left in the common duct. The tube should be inserted in the duct through an opening distal to the site of the anastomosis, to preclude the danger of separating the anastomosis when the tube is pulled out.

In the case in which the ampulla and a portion of the common duct were removed, the section was so small that the common duct could easily be sutured to the wall of the duodenum without transplantation.

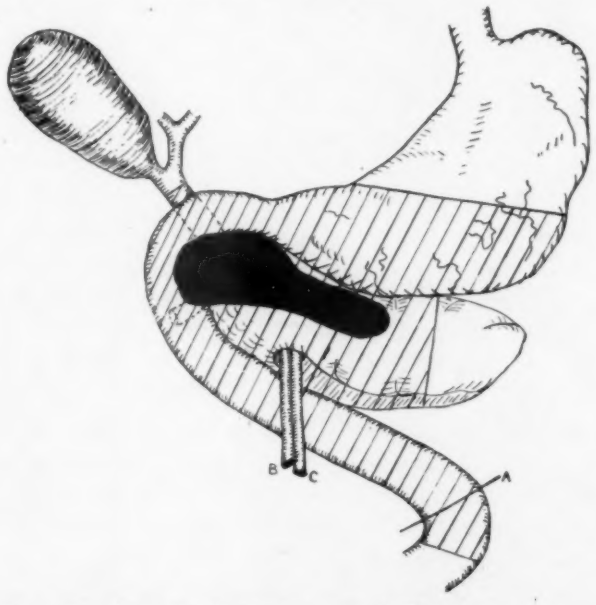

Fig. 1 (case 3).—The deeply shaded area indicates the extent of carcinoma of the pancreas. The lightly shaded area indicates the portion of the stomach, the duodenum, the common duct and the pancreas removed. *A*, ligament of Treitz; *B*, superior mesenteric vein; *C*, superior mesenteric artery.

In view of the fact that the jaundice never completely subsided for eighteen months, it appears that hepatitis with cirrhosis of the liver was an important factor in this case. The degree in which the papilloma of the ampulla contributed to the symptomatology directly or indirectly is problematic. The pathologic condition in the liver being excluded, a case of this type should offer an excellent prognosis for permanent cure.

In a case such as the one in which palliative cholecystojejunostomy was performed, a Rous type of anastomosis is preferable to the loop

type, as the incidence of contamination of the gallbladder with intestinal contents is lessened. Even with the Rous procedure it is advisable to make valves in the jejunal arm to further eliminate this factor, as it seems that food will occasionally enter it otherwise. The time expended, however, to make these valves in a palliative procedure hardly seems justified.

The case in which all but a small portion of the pancreas was removed by a one stage modified Whipple procedure presents several interesting points on which to speculate. From a technical standpoint four modifications are recommended (figs. 1 and 2).

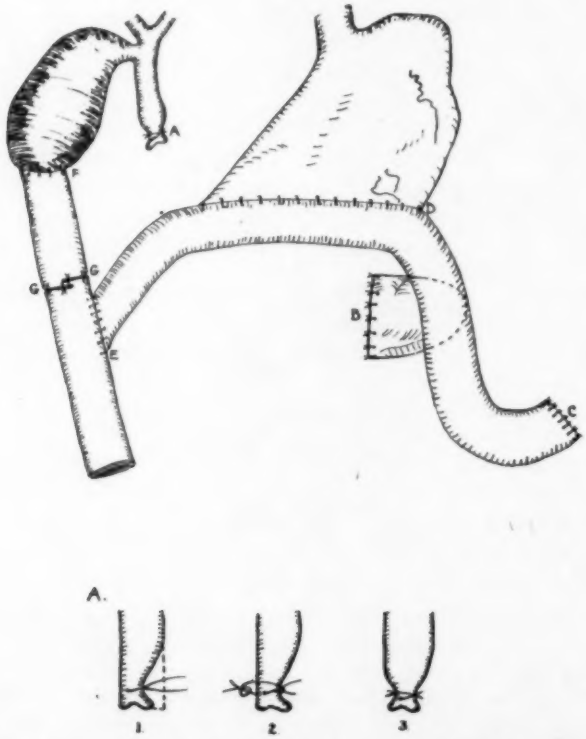

Fig. 2 (case 3).—Completed one stage modified Whipple procedure. *A*, doubly ligated common duct, with the distal suture transfixed to secure the second suture. *B*, sutured capsule of the tail of the pancreas. *C*, sutured blind end of the jejunum. *D*, anterior Polya antiperistaltic gastrojejunostomy. *E*, end to side jejunojejunostomy. *F*, cholecystojejunostomy. *G*, infolding valves to prevent the passage of intestinal contents into the gallbladder.

1. Rather than closure of the end of the stomach and making of a posterior gastrojejunostomy, the jejunum is anastomosed side to end to the open end of the stomach. This is time saving.

2. A so-called antiperistaltic anastomosis is made, so that the distal part of the jejunal loop emerges from the lesser curvature of the stomach

and it is therefore closer to the gallbladder to which it is to be anastomosed. This lessens the pull on the gallbladder resulting from the weight of a long jejunal loop.

3. Anastomosis of the common duct, rather than the gallbladder, to the jejunum has previously been recommended, because of the fatalities which have occurred because the tie on the hugely dilated common duct has slipped or in some way permitted the duct to open. This should not occur if two ties of strong nonabsorbable sutures are used in the following manner: The first tie is transfixed through the wall of the duct with a needle. This suture is tied snugly and the ends temporarily left long. The second tie is not transfixed with a needle but completely surrounds the duct. It is kept in place by tying the remaining long ends of the transfixed ligature around it (fig. 2). This simple procedure, it seems, should prevent fatality from reopening of the ligated end of the common duct. Owing to the proximity of the common duct to the portal vein and hepatic artery, it is technically more difficult to anastomose to the jejunum than is the gallbladder. If the foregoing precaution is taken, it seems that cholecystojejunostomy is preferable to choledochojejunostomy, providing, of course, that the cystic duct is patent.

4. Even when the more desirable Rous principle is utilized in anastomosing the jejunum to the gallbladder, reports suggest that cholecystitis incident to passage of intestinal contents into the gallbladder occasionally occurs. In this case two infolding valves were made in the jejunal arm. This theoretically permits the flow of bile from the gallbladder into the jejunum but hampers the passage of partially digested food upward into the arm beyond the valves. This procedure, it seems, should prevent morbidity from this factor. Warren Cole has recently recommended the placing of two or three valves in the jejunal arm when it is anastomosed at the hilus of the liver following resection of the bile duct because of the extensive stricture.[5]

In the case reported, the patient has presented no symptoms of cholecystitis and is clinically well six months following operation. Evidently a large amount of amylase was liberated into the blood stream after resection of most of the pancreas. This is suggested by a serum amylase level of 800 units on the fifth postoperative day. Three months following operation the serum amylase content was 267 units per hundred cubic centimeters of blood, which is slightly above normal. The pathologic physiology involved is not clear. It is interesting to note that even though only a small portion of the tail of the pancreas remained after operation in this case diabetes did not ensue. The blood sugar content was 73 mg. two weeks after operation, and it is now normal,

5. Cole, W.: Surg., Gynec. & Obst. **82**:104-105, 1946.

six months after operation. Total pancreatectomy in the 8 cases which have been reported is consistently followed by diabetes, which must be carefully controlled by insulin.[4] The patient operated on by Clagett died from a severe reaction to insulin. It therefore seems that total pancreatectomy should not be performed if the sparing of a small portion of the tail of the pancreas does not detract from the realization of an over-all optimum prognosis.

SUMMARY

The scope of surgical procedures applicable to the treatment of obstructive neoplasms of the extrahepatic biliary tract is limited. For all practical purposes, individualization of treatment is confined to four methods, namely, (1) local excision, (2) transduodenal resection of the ampulla of Vater, (3) a Whipple type of procedure and (4) palliative shunting of the bile flow.

Four cases are reported which illustrate the indications for each of these procedures.

Four modifications of the Whipple operation are submitted, which it seems decrease operative time, morbidity and mortality rate.

Sparing a small portion of the tail of the pancreas has prevented postoperative diabetes, whereas total pancreatectomy has consistently been followed by diabetes. It is therefore important in resections of the pancreas to leave some pancreatic tissue intact whenever practical.

HEMODILUTION FOLLOWING EXPERIMENTAL HEMORRHAGE

Influence of Body Movement, of the Ingestion of Water and of Anesthesia Induced by Intravenous Administration of Pentothal Sodium

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ST. LOUIS

DESPITE the large number of studies on hemorrhage, there is little exact information in regard to the phenomenon of hemodilution, this term being used to describe a decrease in the red cell concentration in the blood, as measured by the hematocrit reading, by the erythrocyte count or by the concentration of hemoglobin. While most observers agree that hemodilution (i.e., anemia) ordinarily follows severe hemorrhage, it is generally believed to occur only after the lapse of time. For example, in two textbooks on hematology the hemodilution following a severe hemorrhage is described as follows:

"The red cell count, hemoglobin, and volume of packed red cells, at first misleadingly high as the result of vasoconstriction and of liberation of corpuscles from storehouses such as the spleen, decrease and may continue to fall for several days even though hemorrhage has ceased." [1]

"There will be little or no deviation from normal if an erythrocyte count and hemoglobin determinations are made soon after a hemorrhage . . . . There is a gradual fall . . . during the following hours. This reaches its lowest level after 24 to 72 hours." [2]

Moreover, there is little data as to the factors which influence it. Although hemodilution is presumably a beneficial compensatory mechanism aimed at restoring blood volume, it does so with a protein-poor fluid, which leads to hypoproteinemia. One therefore wonders how decisive a part it plays in the survival from severe hemorrhage.

In the present study, three factors, i. e., body movement, ingestion of water and anesthesia, were studied and found to influence the degree of hemodilution following a single, severe, nonfatal hemorrhage in dogs.

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From the Department of Surgery, Washington University School of Medicine, and Barnes Hospital.

1. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942, p. 391.

2. Fowler, W. M.: Hematology, New York, Paul B. Hoeber, Inc., 1945, p. 160.

PREVIOUS OBSERVATIONS

Probably the first study of the concentration of red cells following a severe hemorrhage was reported in 1854 by Vierordt.[3] Rabbits and dogs were used without anesthesia and prompt decreases found within a few minutes after bleeding. In two experiments a drop exceeding 50 per cent of the initial value was noted within several hours after the removal in intervals of amounts of blood approximating one fourth to one half of the estimated total circulating blood volume. Although a considerable number of experiments have been reported since then, no attempt to review them will be made. Only a few of the more recent observations will be mentioned under the following headings.

Anesthesia.—Experiments reported from this laboratory in 1936 showed that the induction of a general anesthesia with sodium amytal inhibited the hemodilution which occurred in dogs similarly bled under local anesthesia.[4] Three years before this, Adolph, Gerbasi and Lepore [5] compared the effect of ethyl carbamate anesthesia and sodium amytal anesthesia on the red cell concentration following a single hemorrhage of from 20 to 35 cc. per kilogram in 7 dogs. They found an increased concentration of red cells following bleeding in the dogs anesthetized with sodium amytal, not observed in those under anesthesia induced with ethyl carbamate. These authors explained the difference by the discharge of corpuscles from the spleen, which was enlarged and full of blood, due to the effect of sodium amytal, an effect which is not shared by ethyl carbamate. This influence of the barbiturates on the size of the spleen has been observed by others.[6] Of incidental interest is the fact that the aforementioned authors [5] noted that the production of a large store of red cells in the spleen had an apparently beneficial influence inasmuch as dogs anesthetized with sodium amytal withstood more bleedings than those under anesthesia induced with ethyl carbamate. Another observation made by these workers is the fact that the rate of hemodilution was greatly reduced in the absence of the viscera.

In the following studies on hemorrhage, definite differences were observed in hemodilution depending on whether or not a general

3. Vierordt, K. von V.: Arch. physiol. de heilk. **13**:274, 1854.

4. Elman, R.; Weiner, D. O., and Cole, W. H.: Proc. Soc. Exper. Biol. & Med. **32**:793, 1935.

5. Adolph, E. F.; Gerbasi, M. J., and Lepore, M. J.: Am. J. Physiol. **104**:502, 1933.

6. Bourne, W.; Bruger, M., and Dreyer, N. B.: Surg., Gynec. & Obst. **51**:356, 1930. Essex, H. E., and others: Proc. Soc. Exper. Biol. & Med. **35**:154, 1936.

anesthesia was used. For example, Hirota[7] bled rabbits without anesthesia in amounts up to 50 per cent of the estimated blood volume and demonstrated prompt hemodilution as measured by the hematocrit reading, which fell as much as 52 per cent. This investigator also measured changes in blood and colloidal osmotic pressures and was able to show a relationship between the two, confirming the Bayliss-Starling hypothesis. Thus, when blood pressure was high and colloidal osmotic pressure low, little fluid flowed into the blood stream after hemorrhage, so that restoration of blood volume was slight. On the other hand, when the blood pressure was low and the colloidal osmotic pressure high, restoration of blood volume was pronounced, as shown by a decided hemodilution. Boyd and Stevenson[8] found a drop of 25 per cent in the concentration of hemoglobin within three hours after a single hemorrhage equal to 25 per cent of the estimated blood volume in unanesthetized rabbits. Ikeda[9] removed 15 cc. per kilogram of body weight in unanesthetized rabbits and found that both viscosity and red cell count fell within six to twenty-four hours.

Fine, Fischmann and Frank[10] found that anesthesia induced with pentobarbital sodium had a profound effect on the reaction of dogs to a single large hemorrhage (equal to 30 to 40 per cent of the previously calculated blood volume). These animals invariably went into shock, as compared with complete absence of shock in unanesthetized animals. The latter showed pronounced hemodilution, regaining an average of 53 per cent of the lost blood volume in four hours. Although no data on hemodilution were reported in the anesthetized dogs, it is probable that a failure to restore fluid played an important part inasmuch as it was found that recovery from shock, even when present for one-half hour or more, followed the intravenous injection of isotonic solution of sodium chloride or plasma.

Using pentobarbital sodium anesthesia in dogs, Price, Hanlon, Longmire and Metcalf[11] found little change in the hematocrit reading, even though about 35 cc. per kilogram of body weight was bled and all animals succumbed. Magladery, Solandt and Best[12] bled dogs anesthetized with pentobarbital sodium 18 to 68 per cent of the total blood volume, i. e., until the blood pressure reached 30 mm. of mercury. All but 4 died, 5 at the end of the hemorrhage. In all but 3 cases

7. Hirota, K.: J. Biochem. **9**:87, 1928.

8. Boyd, E. M., and Stevenson, J. W.: J. Biol. Chem. **122**:147, 1937.

9. Ikeda, T.: Taiwan Igakkai Zasshi **41**:322, 1932.

10. Fine, J.; Fischmann, J., and Frank, H. A.: Surgery **12**:1, 1942.

11. Price, P. B.; Hanlon, C. R.; Longmire, W. P., and Metcalf, W.: Bull. Johns Hopkins Hosp. **69**:327, 1941.

12. Magladery, J. W.; Solandt, D. Y., and Best, C. H.: Brit. M. J. **2**:248, 1940.

there was no hemodilution; indeed, in 6 the red cell volume rose between the end of the hemorrhage and death. It is of interest, however, that in only 2 animals was hemodilution found, and these lived the longest (two hours) of those that died. No data on changes in hematocrit reading are recorded on the 4 which recovered. That chloroform probably does not inhibit hemodilution was shown by Chevallier and Trabouyer,[13] who, in dogs so anesthetized, observed hemodilution within five to ten minutes following hemorrhage, which, however, always proved fatal. Using morphine only in dogs, Beard, Wilson, Weinstein and Blalock[14] found no spontaneous change in hematocrit value following removal in intervals of 40 cc. of blood per kilogram of body weight. However, if fluids were injected in similar experiments, the hematocrit level fell.

In 8 cats anesthetized with pentobarbital sodium Brown, Miles, Vaughan and Whitby[15] found a progressive hemodilution following successive bleedings of 5 cc. every ten minutes until death occurred. Hemodilution values were parallel as measured by a fall in hemoglobin concentration, red cell count and hematocrit reading. The final value was between 40 and 50 per cent of the initial value.

Although hemodilution was not studied, it is of interest to mention a detailed study on the effect of various anesthetics on the resistance of dogs to severe hemorrhage, as carried out by Zweifach, Hershey, Rovenstine, Lee and Chambers.[16] An initial bleeding of 20 cc. per kilogram of body weight was followed by 5 cc. every thirty minutes until blood flow ceased in a portion of exteriorized omentum. The least deleterious effects were shown by dogs under local and cyclopropane anesthesias. Thus, in them more blood could be removed (53 and 48 cc. per kilogram) and less collapse occurred at the end of three hours (23 and 33 per cent respectively) as compared with those anesthetized with pentothal sodium and pentobarbital sodium, which withstood but 40 and 30 cc. per kilogram and showed collapse in 100 and 75 per cent at the end of three hours respectively.

Influence of Fluid Intake.—That dehydration impairs hemodilution following hemorrhage was demonstrated by Weston, Janota, Levinson

13. Chevallier, A., and Trabouyer, L.: Compt. rend. Soc. de biol. **107:** 1129, 1931.

14. Beard, J. W.; Wilson, H.; Weinstein, B. M., and Blalock, A.: J. Clin. Investigation **11:**291, 1932.

15. Brown, G. L.; Miles, J. A. R.; Vaughan, J. M., and Whitby, L. E. H.: Brit. M. J. **1:**99, 1942.

16. Zweifach, B. W.; Hershey, S. G.; Rovenstine, E. A.; Lee, R. E., and Chambers, R.: Surgery **18:**49, 1945.

and Necheles.[17] In dogs kept without food or water before bleeding, 7 showed a decrease and 8 an increase in the red cell count. By contrast, dogs kept without food but with adequate water before bleeding showed hemodilution in 9 and hemoconcentration in 2. Local anesthesia was used. Calvin [18] noted that dehydration made a striking difference in the degree of hemodilution following a single severe hemorrhage amounting to 25 per cent of the previously calculated blood volume. Dogs deprived of food and water for forty-eight hours previous to hemorrhage exhibited a much smaller drop in hemoglobin content within four hours than similar animals deprived of food but not of water for twenty-four hours previously but given 500 cc. of 0.7 per cent isotonic solution of sodium chloride before bleeding. The type of anesthesia was not mentioned, but was obviously the same in the two groups. In experiments from the laboratory of one of the present authors [19] the ingestion of fluids was shown to increase slightly the ability of dogs to withstand repeated hemorrhage, although no observations were made on its influence on hemodilution.

The Effect of Position.—In a communication from this laboratory the immobile position was found to increase the susceptibility of dogs to repeated hemorrhage.[19] No data, however, were made of whether this influence was associated with any difference in hemodilution. Curiously enough, in normal human beings a fall in plasma protein, as much as 0.8 Gm. per hundred cubic centimeters, due to hemodilution, was found during rest in bed.[20]

Observations Following Hemorrhage in Human Beings.—Ebert, Stead and Gibson [21] observed a fall in the hemoconcentration for seventy hours in human donors following the removal of 760 to 1,220 cc. of blood. Walsh and Sewell [22] observed progressive hemodilution beginning two hours after bleeding 500 cc. in 6 donors, as measured by a fall in hematocrit value and hemoglobin concentration. Wallace and Sharpey-Schafer [23] studied the changes in hemoglobin concentration in 28 human donors bled 500 to 1,150 cc. and found great individual variations. In only 5 was there any hemodilution within one hour. At some time after bleeding, however, all but 5 showed decreases of 10 to 30 per cent from the initial value. The time of maximum dilution

17. Weston, R. E.; Janota, M.; Levinson, S. O., and Necheles, H.: Am. J. Physiol. **138**:450, 1943.

18. Calvin, D. B.: J. Lab. & Clin. Med. **26**:1144, 1941.

19. Elman, R., and Davey, H. W.: Proc. Soc. Exper. Biol. & Med. **56**:14, 1944.

20. Perera, G. A., and Berliner, R. W.: J. Clin. Investigation **22**:25, 1944.

21. Ebert, R. V.; Stead, E. A., and Gibson, J. G.: Arch. internat. de med. **68**:1578, 1941.

22. Walsh, R. J., and Sewell, A. K.: M. J. Australia **1**:73, 1946.

23. Wallace, J., and Sharpey-Schafer, E. P.: Lancet **2**:393, 1941.

in 16 cases occurred within twenty-four hours. Tonkes [24] studied the blood loss following pregnancy and found little hemodilution under three days, whether or not the patients had received isotonic solution of sodium chloride subcutaneously. Browne, Miles, Vaughan and Whitby [15] carefully observed changes in the blood before and at short intervals after bleeding 540 cc. from a donor. The hemoglobin concentration dropped immediately after bleeding, the red cell count one-half hour later and the hematocrit reading not until one and one-half hours later. In a patient estimated to have lost 745 cc. of blood following radical mastectomy, hemodilution was slower in its appearance by several hours but was progressive during four days thereafter.

METHODS

Healthy mongrel dogs between 8 and 10 Kg. in body weight were selected. They were maintained on a normal diet for two weeks before experimentation. A single large bleeding was rapidly carried out from the femoral artery, exposed with the animals under local anesthesia by means of a glass cannula introduced into the lumen, through which an amount of blood was removed equaling 40 cc. per kilogram of body weight. The artery was then ligated and the skin closed with sutures.

Hemodilution was measured by changes in the red cell volume, a 1 cc. hematocrit tube being used, into which heparinized blood was placed after its removal from the femoral vein. Preliminary observations had shown that the same hematocrit readings were obtained from arterial as from venous blood. The heparinized blood was spun at 3,000 revolutions per minute for thirty minutes. This was shown to produce the maximum packing of red cells. The initial hematocrit reading before hemorrhage was taken as 100 per cent, and all subsequent readings were calculated as percentages thereof. Samples were removed at one, three, six, ten and twenty-four hours after hemorrhage.

Five groups of experiments were carried out as follows. 1. Five dogs were immobilized in the supine position for ten hours after hemorrhage, during which time nothing was given by mouth. 2. Five dogs were completely mobile and allowed free body movement for ten hours after the hemorrhage but were given nothing by mouth. 3. Five dogs were completely mobile and allowed free movement for ten hours after hemorrhage, during which time water was allowed ad libitum. 4. Four dogs were treated the same as those in group 1 except that pentothal sodium was given for a period of four hours, beginning one hour after hemorrhage and ending five hours after hemorrhage. 5. Five animals were treated the same as those in group 3 except that during a period of one hour, from the third to the fourth after hemorrhage, pentothal sodium was given intravenously. This length of anesthesia failed to influence the hemodilution curve, which was exactly the same as that in group 3.

After the tenth hour all animals were allowed complete movement in the cage and had access to water ad libitum. The amount of water consumed was measured in each instance.

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24. Tonkes, E.: Zentralbl. f. Gynäk. **56**:2003, 1932.

EXPERIMENTAL FINDINGS

The findings are recorded in the accompanying two charts. In spite of the considerable variation in individual experiments, the following findings seem clearcut. Full mobility with or without the ingestion of water increases greatly the degree of hemodilution as compared with that of the animals immobilized in the supine position for ten hours. The latter showed some hemodilution during this time, but the

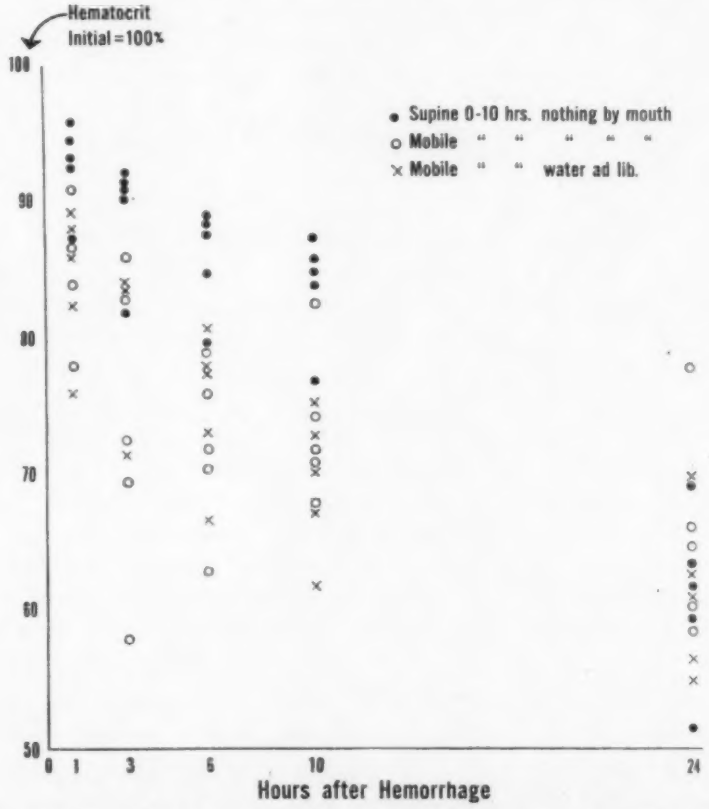

Chart 1.—The effect of mobility and of the ingestion of water. Three groups of 5 dogs each were bled 40 cc. per kilogram of body weight from the femoral artery. Each point represents a hematocrit value. Note that full mobility was followed by the greatest hemodilution. Note also that the hematocrit readings of the mobile dogs allowed nothing by mouth, tended to rise at ten hours, after an early fall. The immobile dogs showed the least hemodilution. Note, however, that, all dogs being allowed full mobility and water ad libitum after ten hours, the hematocrit reading fell to the same level in all groups by the twenty-fourth hour.

hematocrit readings of 4 of the 5 had not fallen below 84 per cent of the initial value, whereas in all but one of the two groups allowed free movement during this period the drop was greater than 75 per cent and in one as low as 62 per cent. In the two groups allowed full

movement, the influence of the ingestion of water is clearly but less strikingly shown. Although the hemodilution up to three and six hours is similar, the red cell volume increased at ten hours in the group of animals given nothing by mouth, thus indicating a reversal of the shift of fluid which entered the blood following the hemorrhage back to the tissues some time between the sixth and tenth hour.

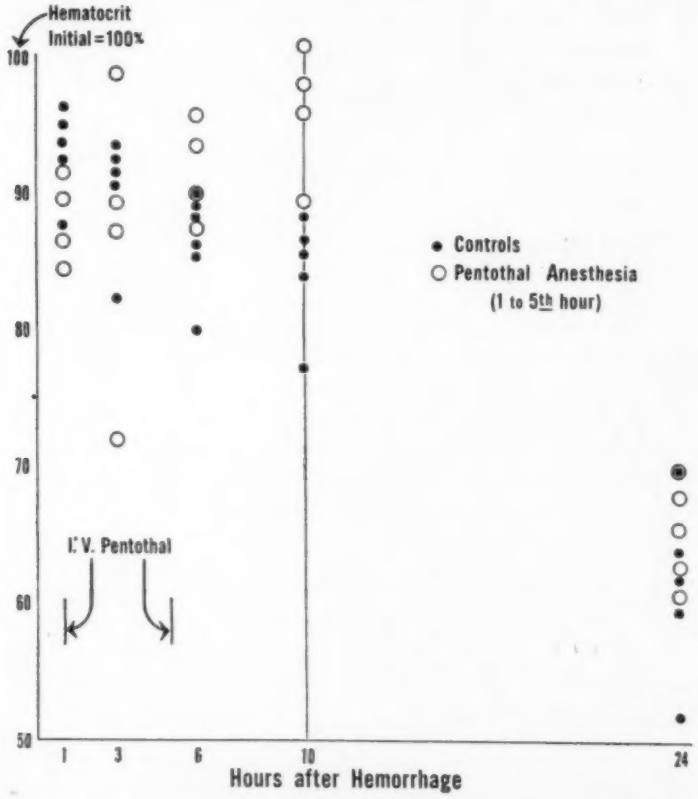

Chart 2.—The influence of pentothal sodium anesthesia. Two groups of 4 dogs each were bled 40 cc. per kilogram of body weight from the femoral artery. Each point represents a hematocrit value. Note the progressive fall in the controls in contrast to the reversal of hemodilution in the anesthetized group, which led at ten hours in 1 case to a value greater than the initial. After ten hours, both groups were allowed full mobility and water ad libitum, the hematocrit value at twenty-four hours being the same in the two groups.

Intravenous administration of pentothal sodium was shown to produce an even greater reversal when given one hour following hemorrhage, at a time when hemodilution had begun. In one experiment the change of fluid shift from the blood to the tissues led to an actual hemoconcentration.

In spite of these variations during the first ten hours, all groups showed the same final degree of hemodilution at twenty-four hours following a period of fourteen hours in which all were allowed full mobility and water ad libitum. This confirms previous findings from this laboratory.[25] The total amount of water consumed was similar in all groups, whether it was taken during the entire twenty-four hour period or only during the tenth to twenty-fourth hour. It varied between 70 and 110 cc. per kilogram of body weight, with the exception of 1 dog, who drank only 35 cc. per kilogram of body weight but whose behavior was in no way different from the others.

The amount of pentothal sodium given was sufficient only to keep the animals asleep. It was found at once that this dose was low as compared with that of the unbled animals. For example, in a normal dog it requires at least 25 mg. per kilogram to maintain anesthesia for one hour. After a hemorrhage of 40 cc. per kilogram, but 17 mg. per kilogram is required to maintain the same degree of anesthesia.

Observations were made on the clinical behavior of all animals after hemorrhage. Those kept immobilized in the supine position, when returned to the cages, were definitely prostrated and lay quietly, gradually reviving and partaking of a large amount of water, so that during the subsequent fourteen hours they consumed as much water as animals in the other groups. None of them, however, showed other symptoms, such as vomiting and diarrhea. By contrast, the dogs returned to the cages immediately after hemorrhage were alert and active, but many of them retched and vomited and many defecated, a few repeatedly in small amounts, and occasionally there was liquid stool. These symptoms rapidly subsided, however, within an hour, and after this time few abnormal clinical manifestations were observed. There were no fatalities.

COMMENT

Considerable variations were observed in the hemodilution curve of many experiments following a standard hemorrhage, even when all conditions were maintained as constant as possible. Much of this variation is undoubtedly due to differences in the physical condition of the animals in spite of the attempt to select those of uniform size, age and nutrition. Moreover, the susceptibility of dogs to hemorrhage must also depend on the initial blood volume, which varies widely. This is important because body weight is not accurately proportional to blood volume. Had we measured each dog's blood volume and used it as the basis to calculate the dose of blood to be removed, the variations might have been less pronounced. Variations in environmental temperature may be important; however, all the present experiments were

25. Elman, R.; Lischer, C. E., and Wolff, H.: Am. J. Physiol. **138**:569, 1943.

done during the spring months, when the indoor air temperature was relatively constant.

In spite of variations, analysis of the graphs presented herewith permits certain definite inferences. Thus, there seems no doubt that the supine, immobile position impairs the ability of fluids to flow into the blood stream, a mechanism which is undoubtedly an attempt to restore the lowered blood volume. Moreover, this impairment is immediately dissipated, even after ten hours of immobility, when the animal is allowed to move about and ingest sufficient water. If the animal is allowed complete movement from the beginning, the influence of the ingestion of water seems of added significance because the progressive hemodilution initially present is not maintained or even reversed when water is withheld.

The influence of position and movement of the body on the fluid shift after hemorrhage may have an important practical bearing when one is considering the advisability of ambulation in patients after injury or operation associated with severe loss of blood. The influence of the ingestion of water is of similar significance. Inferences would depend on whether the best compensated hemorrhage is associated with the greatest degree of hemodilution. On theoretic grounds, the restoration of blood volume by a flow of fluid into the blood would seem to be of obvious compensatory value. Unfortunately, this fluid is free not only of red cells but also of plasma protein. It is interesting, therefore, to speculate as to whether the anemia and hypoproteinemia produced by hemodilution may not do more harm than good, especially when it is pronounced.

From the observations of others, as already cited, hemodilution in general was associated with a more favorable outcome. Experiments are now under way in the attempt to add further data on the exact relationship between the degree of hemodilution and the mortality rate. In a few experiments in which death followed a simple, severe hemorrhage, we have already noted a conspicuous terminal change from hemodilution to hemoconcentration.

The influence of intravenous administration of pentothal sodium in producing hemoconcentration after the initial hemodilution seems striking and unequivocal. If hemodilution is looked on as a beneficial compensatory mechanism, obviously pentothal sodium must be considered as exerting a deleterious influence. With one possible exception [5] most of the observers in experiments already described found that the administration of barbiturates is deleterious during hemorrhage. Pentothal sodium obviously has a profound influence on the movement of fluids after hemorrhage; further study is certainly indicated in view of the widespread use of this agent.

CONCLUSIONS

Hemodilution promptly appeared within one hour, and it persisted up to twenty-four hours following a single, severe (40 cc. per kilogram), nonfatal hemorrhage produced under local anesthesia in dogs. The greatest degree of hemodilution occurred when full mobility and free access to water were allowed immediately after hemorrhage. Immobility in the supine position inhibited the degree of hemodilution. The withholding of water during full mobility tended to change hemodilution to hemoconcentration.

Pentothal sodium given intravenously after the start of posthemorrhagic hemodilution reversed the process and even led to actual hemoconcentration. After hemorrhage, dogs require a much smaller dose of pentothal sodium to maintain anesthesia.

TRAUMATIC AND AMPUTATION NEUROMAS

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AND
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THE CAUSE of painful and traumatic neuromas is not clearly understood. The investigation reported in this paper has been undertaken with the hope of determining whether or not the various methods of dealing with the divided nerve ends influence their occurrence or prevention. The records of the Laboratory of Surgical Pathology have been examined for proved cases, and these as well as amputations of major extremities in the Presbyterian Hospital from 1932 to 1945 were reviewed. Only records with adequate follow-up were used.

DEFINITION

After section, the distal end of the nerve may enlarge and simulate a tumor. These enlargements, called neuromas, are not true neoplasms. The nodule is made up of granulation tissue through which many strands of regenerated or proliferated axons with Schwann sheaths pass. These are arranged in interlacing bundles running in all directions. It is believed that the granulation tissue preceding neuroma formation arises from the blood vessels of the endoneurium and perineurium of the involved nerve as well as from the adjacent soft tissues.

REVIEW OF CASES

Traumatic Neuromas.—An analysis of these records showed that there were sixty-two neuromas following trauma in 61 patients. Pain was the most prominent symptom in 41 cases, anesthesia in 24 and paralysis in 17. Most patients had several complaints. There were 36 men and 25 women.

The fourth decade had the greatest incidence, with 16 cases, and the third decade ranked next, with 15; the older groups had fewer cases. Thus, 50 per cent of the neuromas in this group occurred in the third and fourth decades, corresponding to the period of greatest exposure to industrial hazards. This study includes 56 white, 4 Negro and 1 Chinese patient. Symptoms existed from two months to more than twenty years.

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The common exciting factor in these cases of neuroma was trauma. A frequent story was that the patient pushed his hand through a window or fell on a broken bottle and cut his wrist. Industrial hazards associated with punch presses, stamping machines and choppers are common causes. Frequently an incomplete examination of the extremity resulted in the failure to recognize neural injury. In some, the injury was discovered but an inadequate surgical repair was performed. Thirty cases occurred in the two mentioned groups. In 15 the neuroma followed amputation. These will be discussed separately. In 9 the neuroma occurred after fractures, in 6 after compound fractures, in 2 after the simple type with open reduction and in 1 after a simple type with closed reduction. Mastoidectomy, thyroglossal cystectomy, cholecystectomy, radical mastectomy and other operations each preceded the neuroma in 1 or 2 cases.

Treatment consisted, first, in a detailed examination of the patient's disability and the determination of the nerve or branches involved. The location of a point of maximum tenderness was marked on a diagram, the wound was then explored, the neuroma excised and a neurolysis and neurorrhaphy performed. Fine silk sutures through the epineurium or perineurium were used to maintain the anastomosis. Often, a tenolysis and tenorrhaphy of the adjacent tendons was performed. A plaster cast or splint was utilized as external immobilization to hold the repaired structures in position.

Of the sixty-one neuromas, forty-six followed trauma and fifteen followed amputation. Of the forty-six following trauma, four showed excellent results, with recovery of full sensation and full motion without pain. Twenty-seven patients had a good result, with improved sensation and motion and no pain. Four had a fair result, with improved sensation, motion and some pain. In 2 cases there was little or no improvement. There were no recurrences. Nine cases could not be followed.

Of the 15 cases of neuroma following amputation, results of excision were good in 7, fair in 3 and poor in 3, and 2 patients died soon after the operation of intercurrent disease. Four of the neuromas occurred after amputations of fingers, leaving eleven which occurred after amputations of a major extremity. Three of these were performed in this hospital and the others elsewhere.

Neuromas After Amputation.—From 1932 to 1945, there were 67 patients who had eighty-six amputations. The patients dying soon after operation are not included. There were 45 men and 22 women who had amputations. The highest incidence of amputations occurred in the sixth, fifth and seventh decades, in that order. This series includes a large number of patients whose extremities were amputated for vascular disease or infection following vascular trauma.

Amputation was performed for arteriosclerotic gangrene in 30 cases, neoplasm in 12, arteriosclerotic gangrene with diabetes in 11, compound fractures in 9, thromboangiitis obliterans in 8 and embolism in 6. Seven amputations were done for uncontrollable ascending infection, two for neurotrophic ulcers, one for ruptured iliac aneurysm, with resulting gangrene of the lower extremity, and one for progressive myositis ossificans.

The amputations were done by or under the supervision of seventeen attending surgeons. Local infiltration or spinal or general anesthesia was used, depending on the patient's condition. Refrigeration was used in 2 instances.

In this analysis, all the nerves cut at the same level are recorded as if they were one nerve. Thus, for example, in amputation of a single leg, the peroneal, anterior tibial and posterior tibial nerves have been considered as a unit.

These nerves in different cases were treated by various technics. Into some procaine hydrochloride was injected and they were ligated and transected at the same or higher levels; into others procaine hydrochloride and alcohol was injected, and they were ligated and then divided. Some were transected and received no other treatment. Others were transected and ligated. In the true guillotine amputation only transection was done. Injection of procaine hydrochloride prior to section was done thirty-two times in connection with some other procedure. Injection of alcohol was used fifty-three times. In 50 cases, the nerve was isolated, pulled down, ligated, sectioned and then allowed to retract to a higher level.

Fifty-four amputations gave good results, with a well healed stump and no pain or tenderness. Fair results were obtained in 15 cases and poor results in 17 cases, because of painful or unhealed stumps. Three neuromas occurred in eighty-six amputations done in this hospital. Each of these occurred in patients who had a true guillotine amputation for ascending infection in which the nerve was only transected at the same level. In these cases, wound healing was facilitated by skin traction or skin grafting. In other cases of true guillotine amputation, a revision or reamputation of the stump was performed, the nerve was ligated and sectioned at a higher level and no neuromas resulted. In cases in which neuromas were removed at this hospital after amputation elsewhere, a history of guillotine amputation or infection was elicited. In our 3 cases, the amputation neuroma was excised at a higher level, the nerve was placed in normal soft tissues and no further neuroma resulted.

COMMENT

Traumatic Neuromas.—The experience at the Presbyterian Hospital with neuromas after trauma is in agreement with the experiences elsewhere. The importance of a careful examination of a patient who

has an injury in the vicinity of a nerve cannot be overemphasized. Even if the point of entry of a sharp instrument is not immediately over the nerve, a careful local neurologic examination of both the sensory and the motor components should be done. This has been stressed by Stoney,[1] Coleman,[2] Spurling [3] and others. The theories and mechanisms in nerve healing, regeneration and formation of neuromas were described by Gurdjian and Smathers,[4] Weiss,[5] Davis and Hiller [6] and others.

As soon after the injury as possible, the severed nerve ends should be debrided and sutured together end to end, either fine silk or tantalum wire sutures being used. If there is an absence of nerve tissue, prohibiting primary anastomosis, the nerve should be mobilized by dissecting up the extremity, so that by flexion of the adjoining joints the nerve ends may be approximated. The extremity should then be held in position by some means of external immobilization.

If a primary repair is impossible within approximately six hours, ten to fourteen weeks should be allowed to elapse before neurorrhaphy. Electric stimulation of the muscles which are normally innervated by the injured nerve must be used to preserve normal muscle tone and contractility. The use of tantalum and other inert suture material may decrease the occurrence of granulation tissue, which aids in the formation of a neuroma.

The neuroma, once formed, should be dissected from the surrounding tissues and excised in slices proximally and distally until normal nerve fasciculi are seen. The nerve ends should then be sutured and, if possible, placed in a new area of soft tissue. A transplant of fat or tantalum foil around the site of anastamosis may prevent adhesions.

Neuromas After Amputation. — The most interesting group of neuromas gathered in this series is that in which the growth occurred after amputation. Fifteen cases were found in this group. Three of these followed amputations in this hospital and occurred after a true guillotine amputation. After this procedure, stump closure may be

1. Stoney, R. A.: Forty Years' Experience with Nerve Suture, Irish J. M. Sc., March 1944, pp. 85-92.

2. Coleman, C. C.: Peripheral Nerve Surgery: Diagnostic Considerations, J. Neurosurg. **1**:123-132 (March) 1944.

3. Spurling, R. G.: Symposium on War Surgery: Use of Tantalum Wire and Foil in Repair, S. Clin. North America **23**:1491-1504 (Dec.) 1943; Nerve Surgery: Technical Considerations, J. Neurosurg. **1**:133-138 (March) 1944.

4. Gurdjian, E. S., and Smathers, H. M.: Peripheral Nerve Injury in Fractures and Dislocations of Long Bones, J. Neurosurg. **2**:202-219 (May) 1945.

5. Weiss, P.: Sutureless Reunion of Severed Nerves with Elastic Cuffs of Tantalum, J. Neurosurg. **1**:219-225 (May) 1944; Technology of Nerve Regeneration, ibid. **1**:400-450 (Nov.) 1944.

6. Davis, L., and Hiller, F.: Regeneration in End to End Suture, Grafts, and Gunshot Injuries, Tr. Am. Neurol. A. **70**:178-179, 1944.

aided by traction on the skin or by skin grafting and the stump later revised in such a way that the nerve lies at a level higher than the scar.

A study of the neuromas removed in this hospital after amputations elsewhere showed that they resulted from similar causes. In most guillotine amputations performed at this hospital, the wound was allowed to heal assisted by skin traction or grafts, and later the stump was revised. No neuromas occurred in this revised group. Thus, it seems that neuromas and tender stumps arise oftener after a true guillotine amputation or when infection is present or develops soon after the procedure in such a way that the nerve is included in the scar tissue. This does not happen in the so-called modified guillotine amputation used at this hospital (Smith [7]).

The symptoms of these neuromas are characteristic. They are produced by pressure, irritation of the area or movement of the scar tissue and are described as radiating down the former distribution of the nerve often being relieved by the local infiltration of procaine hydrochloride. White [8] suggests that the pain may be due to stimuli from the neuroma or from the sensory areas of the cerebral cortex. Repeated ill advised surgical procedures to rid the patient of his complaints may intensify rather than alleviate the symptoms. Spurling [8] and Boldrey [9] list the harmful and the advised methods of treatment.

The phantom limb syndrome occurred in only 3 patients with amputations. Of these, not one had a palpable neuroma.

This review suggests that the treatment of nerve ends is of importance in the prevention of a neuroma. The nerve should not be allowed to be included in the scar tissue which follows the operation. Following the technics used in the Presbyterian Hospital, there were only three neuromas. A review of the literature suggests that injection of alcohol into the nerve is harmful rather than helpful. Experimental work of Huber and Lewis showed delay in the regeneration of nerve fibers after injection of alcohol, but other reports have not shown a significant decrease in the frequency or size of neuromas or decrease in the pain or incidence of the phantom limb with this procedure alone. Livingston [10] and Bate [11] do not favor injection of alcohol.

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7. Smith, B. C.: Amputation Through Lower Third of Leg for Diabetic and Arteriosclerotic Gangrene, Arch. Surg. **27**:267-295 (Aug.) 1933.

8. White, J. C.: Pain After Amputation (Especially Due to Neuroma and Phantom Limb) and Its Treatment, J. A. M. A. **124**:1030-1035 (April 8) 1944.

9. Boldrey, E.: Amputation Neuroma in Nerves Implanted in Bone, Ann. Surg. **118**:1052-1057 (Dec.) 1943.

10. Livingston, K. E.: Phantom Limb Syndrome: Discussion of Role of Major Peripheral Nerve Neuromas, J. Neurosurg. **2**:251-255 (May) 1945.

11. Bate, J. T.: Method of Treating Nerve Ends in Amputation Stumps, Am. J. Surg. **64**:373-374 (June) 1944.

There are numerous ways of treating nerve ends. Boldrey [9] reviewed the older methods and suggested one of his own. Herrmann and Gibbs,[12] Weiss,[5] Spurling,[3] Poth [13] and others have suggested various treatments of nerve ends to prevent neuromas.

This study suggests that the best method of preventing a neuroma after amputation is the isolation of the nerve from the surrounding tissue, the nerve being gently pulled down so as to permit retraction into normal soft parts, and ligation with some nonabsorbable material such as silk or tantalum wire. The ligature should be placed with enough tension to prevent bleeding but not to cut through the perineurium. The nerve should be sectioned below the ligature and allowed to retract into the soft tissues without necessarily injecting anything into the nerve.

CONCLUSIONS AND SUMMARY

1. The cases of traumatic neuromas from the records of the Presbyterian Hospital, New York, are reviewed. The commonest causes of neuromas of this type are either failure of the examining physician to recognize a nerve injury or else a poor reparative procedure.

2. The amputations done on major extremities are also reviewed. In eighty-six amputations done at the Presbyterian Hospital only three neuromas occurred.

3. The occurrence of the neuroma seems to be associated with infection or inclusion of the nerve in scar tissue. Tender stumps and neuromas occur less frequently when a reamputation or revision of the stump is carried out.

4. The best method of prevention at present seems to be ligation and section of the nerve as high as possible above the level of amputation, so that the nerve end is embedded in soft tissue and not in dense scar tissue. Nothing need be injected into the nerve with the idea of prevention of growth.

Dr. Beverly C. Smith assisted in the preparation of this paper.

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12. Herrmann, L. G., and Gibbs, E. W.: Phantom Limb Pain: Relation to Treatment of Large Nerves at Time of Amputation, Am. J. Surg. **67**:168-180 (Feb.) 1945.

13. Poth, E. J., and Fernandez, E. B.: Prevention of Neuroma Formation by Encasement of the Severed Nerve End in Rigid Tubes, Proc. Soc. Exper. Biol. & Med. **56**:7-8 (May) 1944. Poth, E. J.; Fernandez, E. B., and Drager, G. A.: Prevention of Formation of End-Bulb Neuromata, ibid. **60**:200-207 (Nov.) 1945.

AIR IN THE BILIARY PASSAGES

A Review and Report of a Case

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OUR BELIEF is that the future success in the diagnosis of internal biliary fistula lies not in roentgenologic examination exclusively but more in evaluation of the pathologic antecedents that accompany the biliary fistula. With more emphasis placed on clinical study of cases of biliary disease, a greater number of biliary fistulas will be recognized earlier, thus minimizing future complications, and with more attention to the preoperative care the present mortality rate following operations on internal biliary fistulas will be reduced.

Spontaneous internal biliary fistulas are infrequent. The majority result from infections and calculi in the gallbladder or are caused by a perforative ulcer or a malignant growth of the stomach or bowel. According to the literature, in only 108 cases have internal biliary fistulas been recognized preoperatively, and all have been diagnosed by roentgenologic examination. Of this number, including our case, in only 12 cases has diagnosis been made by visualization of air or gas alone in the biliary passages.

The diagnosis of this type of fistula and the high death rate the fistula carries are the most important features of any discussion on internal biliary fistula. Because of certain characteristics all fistulas possess, as pointed out in the paper, in only a small percentage of cases will the roentgenologic examination be of any value in the diagnosis. A review of the literature indicates that little thought has been given to the value of presumptive diagnosis based on pathologic antecedents, which may include elimination of a large stone by the bowel, acute paralytic ileus or spontaneous diarrhea occurring during a well defined biliary colicky attack, chronic diarrhea associated with frank biliary symptoms, attacks of pain of biliary nature followed with chills and fever and low grade jaundice or acute intestinal obstruction caused by impaction of a large gallstone in the lower end of the ileum.

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Some of the biliary antecedents are of major importance, especially passage by the rectum of a gallstone of such size that it could not have escaped the normal route by the ampulla and the chronic diarrhea associated with typical biliary symptoms. On a presumptive diagnostic basis the patient in our reported case presented several pathologic antecedents: spontaneous diarrhea, which occurred at the time of the development of the fistula, and acute biliary colicky attacks of pain followed by chills, fever and jaundice.

INCIDENCE

There appears to have been considerable variation in the incidence of internal biliary fistulas in different periods. During the nineteenth century, Courvousier [1] and other writers on this subject found a greater incidence than has been reported during the past three decades. Roth,[2] of Basel, Switzerland, sectioned 166 patients who had died from gallstones during the nine year period from 1872 to 1881, and in this number he found 14 patients who had had either recent or old perforations of the gallbladder or bile ducts. Courvousier reported an incidence of 4.8 per cent of biliary fistulas at autopsies of patients who died from gallbladder disease during the six year period from 1882 to 1888. Only rarely was a correct diagnosis of internal biliary fistula made during life; hence the lack of proper treatment probably accounts for the high death and autopsy rates at this early period. In the past three decades the reported incidence of internal biliary fistulas has been lower. For the twenty-four year period from 1915 to 1939, Dean [3] found only 1.2 per cent of chronic infections of the gallbladder to be complicated by internal biliary fistulas. Puestow [4] reported finding 16 cases of internal biliary fistulas in five hundred operations for benign disease of the biliary tract, an incidence of 3.2 per cent. This smaller incidence of internal biliary fistulas in recent decades is probably the result of earlier diagnosis and improved methods of surgical treatment of chronic disease of the gallbladder.

ETIOLOGY

Infection and calculi in the biliary tracts are responsible for production of the greatest number of internal biliary fistulas.

The inflammatory process in the biliary system results in formation of adhesions between the involved viscus and neighboring organs. Because of the anatomic position, the frequency of involvement is in the following order: duodenum, colon and stomach. Pressure from a

1. Courvousier, L. G.: Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege, Leipzig, F. C. W. Vogel, 1890, pp. 83-114.

2. Roth, cited by Courvousier.[1]

3. Dean, G. O.: Internal Biliary Fistulas, Surgery **5**:857-864 (June) 1939.

4. Puestow, C. B.: Spontaneous Internal Biliary Fistula, Ann. Surg. **115**: 1043-1054 (June) 1942.

stone against the inflamed wall of the gallbladder produces erosion and necrosis and leads to perforation. This may then result in one of the following conditions: the formation of a walled-off fistula between the gallbladder and the other involved viscus, with spilling of septic gallbladder contents into the bowel; formation of a pericholecystic abscess, or perforation into the free peritoneal cavity, with the development of generalized peritonitis.

Other less common causes of internal biliary fistula are perforated duodenal ulcer, neoplasms of the stomach or gallbladder and hydatid infestation.

Pataro,[5] Garland and Brown [6] and others stated that when the fistula is between the common duct and the duodenum it is almost always the result of a perforated duodenal ulcer. Murchison,[7] working before the days of roentgenologic examinations, expressed the opinion that fistulas between the gallbladder and the colon usually resulted from malignant growths, whereas Stevenson and Sherwood [8] reported in 1940 that in 5 such cases in which diagnosis was made roentgenologically in this country, all were the result of infection and calculi. There is disagreement as to whether chronic phlegmonous cholecystitis without stones may produce a fistula.

PATHOLOGY

The pathologic changes of internal biliary fistula consist of extensive adhesions involving the bowel, gallbladder and liver. The gallbladder is contracted, thickened and fibrotic and may or may not show additional stones. The cystic duct is usually open and may be enlarged. The common duct is frequently blocked in its lower end by a stone, with resultant dilatation of the common and hepatic ducts and biliary radicles. Hepatitis may result from spread of intestinal contents through the fistula and biliary system into the hepatic substance. The fistulous tract itself may vary in size and may remain patent or become closed.

Intestinal obstruction may occur when a large stone becomes impacted in the terminal ileum or when a paralytic ileus results from periduodenal inflammation. The inflammatory type of obstruction usually occurs during development of the fistula as a result of one of the fol-

5. Pataro, F. A.: La diarrea como síntoma de presunción diagnóstica de las fistulas biliares internas, Semana méd. **2**:524-535 (Sept. 2) 1943.

6. Garland, L. H., and Brown, J. M.: Roentgen Diagnosis of Spontaneous Internal Biliary Fistulae, Especially Those Involving the Common Bile Duct, Radiology **38**:154-159 (Feb.) 1942.

7. Murchison, C.: A Clinical Lecture on Diseases of the Liver, Jaundice and Abdominal Dropsy, edited by T. L. Brunton, London, Longmans, Green & Co., 1885, p. 569.

8. Stevenson, C. A., and Sherwood, M. W.: The Roentgen Diagnosis of Cholecystocolic Fistula, Radiology **35**:616-621 (Nov.) 1940.

lowing mechanisms: paralytic ileus due to local peritonitis; volvulus of the small bowel induced by the violence of the gallstone colic; reflex spasm secondary to the passage of the stone through the newly formed fistulous tract, or a result of adhesions. This type of obstruction is more commonly seen when the fistula is of the biliary-duodenal type. Four cases of inflammatory obstruction of this type have been reported by Bengolea and Suárez.[9]

CLINICAL MANIFESTATIONS

The clinical manifestations of internal biliary fistula are similar to those usually seen in chronic biliary disease, except that they are severer. Colicky pains, jaundice, chills and fever are the signs oftenest seen. Frequently there is obstruction of the common bile duct with the symptoms usually related to such obstruction. Diarrhea probably occurs more frequently in spontaneous internal biliary fistula than has been reported in the literature. When diarrhea occurs in association with other symptoms of biliary disease, the existence of a biliary fistula should be suspected. An acute or sporadic form of diarrhea may occur in cholecystoduodenal fistula and is believed to be secondary to the sudden spilling of the septic contents of the gallbladder into the intestine at the time of fistulous formation. A chronic form of diarrhea may occur in the cholecystocolic type of fistula, in which the bile reaches the colon in an unoxidized form and produces a hyperperistalsis by its irritant effect on the mucosa of the colon. Intestinal obstruction has been mentioned before; its presence in a patient with symptoms or history of biliary disease should arouse suspicion that a biliary fistula has formed.

Many internal biliary fistulas are asymptomatic owing to the fact that they remain open to provide adequate drainage. Oftener the fistula contracts because of inflammation and fibrosis, resulting in a return of the symptoms of obstruction of the common duct, namely, chills, fever and jaundice. It has often been asserted that formation of a fistula is nature's cure for an obstruction of the common bile duct. However, the other features connected with formation of a fistula, such as the complications mentioned and the high mortality rate associated with surgical cure, would seem to make the "cure" worse than the disease.

ROENTGENOLOGY

With improvement in roentgenologic diagnosis and increase in the number of patients having roentgenologic studies made for gallbladder and other gastrointestinal complaints, more likely a greater number of internal biliary fistulas will be recognized by roentgenologic examination in the future. More fistulas are not recognized by roentgenologic

9. Bengolea, A. J., and Velasco Suárez, C.: Las fistulas bilares internas; contribucion a su estudio, Rev. med.-quir. de pat. fem. 7:125, 1936.

examination because in biliary fistulas, as in other fistulas, after the immediate spill of the retained secretions and the back pressure of the blocked channels have been taken care of by formation of the fistula, the fistula in a short time will begin to contract from the inflammation and fibrosis. The life of a fistula in its original size is short. The activity of the fistula will depend largely on retained stones or formation of new stones in the gallbladder and the degree of blockage of the common duct. Consequently, fistulas of large size and recent development will more likely permit the influx of the barium sulfate into the biliary tree during a roentgenologic study after a meal of barium sulfate than a fistula of long duration which has become fibrosed. The visualization of air or gas in the biliary tree is due not so much to size of the fistula as to infection in the biliary tree.

Garland and Brown reported that in 1942 they found 85 cases of spontaneous internal biliary fistulas recorded as having been diagnosed by roentgenologic examination. With this number they reported 5 additional cases. Of this series of 90 cases of internal biliary fistula, in only 9 cases was the presence of air or gas alone revealed in the biliary passage. Of the remainder of the cases, in 76 diagnosis was made by influx of barium sulfate and in the other 5 cases diagnosis was made by both influx of barium sulfate and visualization of air.

From 1941 through 1944, there were 17 cases of internal biliary fistulas diagnosed roentgenologically and recorded. In only 2 of these cases was air or gas alone revealed in the biliary ducts and hepatic radicles. In 2 other cases both influx of barium sulfate and visualization of air were revealed. In the remainder of cases only influx of barium sulfate was revealed.

In this last review of reported cases, the 14 cases of acute intestinal obstruction, caused by impaction of a gallstone, as reported by Rigler, Borman and Noble[10] were not included. They declared that roentgenologic study of the abdomen revealed the presence of air or gas or the influx of barium sulfate in the biliary tree in all cases except 1. The reason for omitting these 14 cases was that their point of discussion was directed primarily toward the acute intestinal obstruction resulting from gallstone impaction and not to the fistula itself, as the findings were merely coincidental. Obviously, the general impression is that if a gallstone has attained size sufficient to block the lumen of the small bowel, it will rarely make its escape through the normal route by the ampullae but instead will escape into the bowel through a fistulous tract originating in the gallbladder or one of the bile ducts.

10. Rigler, L. G.; Borman, C. N., and Noble, J. F.: Gallstone Obstruction: Pathogenesis and Roentgen Manifestations, J. A. M. A. **117**:1753-1759 (Nov. 22) 1941.

The table gives the number of cases of internal biliary fistulas diagnosed by roentgenologic examination, the number of cases which revealed presence of air or influx of barium sulfate into the biliary passages and the name of the author.

MORTALITY

The mortality rate following operation for spontaneous internal biliary fistula is greater than that seen in operations for chronic benign cholecystic diseases. In the latter group of uncomplicated cases, rarely will

Use of Air or Barium in Diagnosis of Biliary Fistula.

Year	Author	Cases	Air or Barium Sulfate
1942	From survey of literature made by Garland and Brown [6]	85	Air: 9 cases Barium sulfate: 76 cases
1942	Garland and Brown [6]	5	Failed to state how many of the cases revealed air or influx of barium sulfate into the biliary passages
1941	Eliason and Stevens [11]	1	Clinical finding based on chronic biliary disease complicated by acute intestinal obstruction from gallstone
1941	Rigler, Borman and Noble [10]	14	Failed to state how many of the cases revealed air or influx of barium sulfate into the biliary passages
1942	Tracey, M. L., and McKell, D. M., Jr.: S. Clin North America **23**: 717, 1943	5	Air: 1 case Barium sulfate: 4 cases
1942	Puestow, C. B.: Ann. Surg. **115**: 1043, 1942	2	Barium sulfate
1942	Delano, P. J.: Am. J. Roentgenol. **47**: 298, 1942	1	Barium sulfate
1942	Taylor, W. B.: Canad. M. A. J. **47**: 332, 1942	2	Barium sulfate
1943	Santora, P. J.: Radiology **41**: 74, 1943...	1	Barium sulfate
1943	Pataro [5]	2	Air: 1 case Barium sulfate: 1 case
1944	Slanger, A.: Rev. Gastroenterol. **11**: 409, 1944	1	Barium sulfate
1944	Brandel, E.: Acta radiol. **25**: 333, 1944...	2	Air: 1 case Barium sulfate: 1 case
1946	Donald, Meadows and Silbermann	1	Air

the surgical mortality rate exceed 1 to 3 per cent, whereas in operations for internal biliary fistula the mortality rate often reaches an alarmingly high figure. Dean reports a mortality rate of 52 per cent. He stated that out of 25 patients with internal biliary fistula operated on 13 patients died after operation. Eliason and Stevens,[11] reporting from a smaller series, stated that 3 of the 5 patients with internal biliary fistula operated on died, yielding a mortality rate of 60 per cent.

11. Eliason, E. L., and Stevens, L. W.: Spontaneous Internal Biliary Fistula, Am. J. Surg. **51**:387-392 (Feb.) 1941.

There are several factors responsible for the high death rate following operation for cure of internal biliary fistula: 1. The age incidence in which internal biliary fistulas are most frequently seen is important. Judd and Burden,[12] after a survey of 153 cases of internal biliary fistula, found the average age to be in the sixth decade. Many patients at this age will present evidence of degenerative changes in the cardiovascular and renal organs, which, if present, will likely influence the surgical picture following any major operation. 2. The type of pathologic condition which is responsible for formation of the fistula is an important factor. It is true that the greater number of internal biliary fistulas result from infections and trauma of the calculi, but there is a small group of cases in which the fistula follows a perforation of a carcinoma of the gallbladder or stomach. In either location in which the carcinoma is present and fistula develops, any operative procedure instituted for correction of the fistula or cure of the malignant growth is followed by a high death rate. 3. Other factors are the local changes in tissue occurring at the site of the fistula, which may encourage operative complications, and, too, the hepatic damage in the form of hepatitis which the fistula produces from escape of the intestinal contents into the bile ducts and biliary radicles. These last two conditions probably are the greatest factors in the high mortality rate seen in operations for internal biliary fistula. Finally, because of present day methods of diagnosis, which is chiefly by roentgenologic examination, only a small percentage of internal biliary fistulas are recognized preoperatively, and as a result the majority of these patients do not receive adequate preoperative care and are not able to meet the demand that a prolonged technical operative procedure for the cure of internal biliary fistula requires (hence, desire for preoperative diagnosis).

TREATMENT

The surgical treatment of internal biliary fistula is much more difficult than that of ordinary biliary disease. The gallbladder, biliary ducts, fistula and intestine are all usually surrounded by a mass of adhesions. The gallbladder is usually found contracted and fibrotic and contains necrotic material. The bowel wall around the fistula is indurated and fibrotic, and, after removal of the fistulous stoma, the lumen of the bowel may be so small as to threaten obstruction and require a gastroenterostomy. Even after the fistula is successfully removed and the opening of the bowel is closed, there still remains the problem of dealing with an obstructed and dilated common bile duct. Obviously, cases in which conditions are diagnosed preoperatively and in which patients can be properly prepared for such extensive operation will be followed by

12. Judd, E. S., and Burden, V. G.: Internal Biliary Fistula, Ann. Surg. **81**: 305-312 (Jan.) 1925.

a lower mortality rate than those in which the fistula is found for the first time on the operating table.

REPORT OF A CASE

The patient was a 52 year old white man, a railroad worker, who had had periodic attacks of acute pain and soreness in the right upper quadrant of the abdomen, accompanied with vomiting, chills and fever, jaundice and diarrhea. The first attack occurred thirteen years before admission and lasted about three weeks. He was relatively symptom free for five years, after which he had a

Fig. 1.—Following ingestion of dye (priodax), the roentgenogram revealed a nonfunctioning gallbladder and air in the common and hepatic ducts and biliary radicles.

second attack similar to the first, except for absence of diarrhea. During the next eight years he had several more attacks. During the last six months previous to admission, the attacks came so frequently that he hardly recovered from one before another one began. For approximately eight years before admission he had been under treatment for diabetes mellitus. This had been adequately controlled by diet and protamine zinc insulin. At the time of admission, he had been suffering about two weeks from his latest attack. He had low grade jaundice, a septic type of temperature and a moderate amount of pain in the right upper quadrant of the abdomen. The stools were normal in color, and physical exami-

nation was noncontributory except for tenderness and moderate rigidity in the right upper quadrant, moderate jaundice and absence of the right leg at the mid-thigh (following amputation for a complicated fracture).

Laboratory data were as follows: hemoglobin content, 9 Gm. (58 per cent); red blood cells, 3,790,000 per cubic millimeter; white blood cells, 9,400 per cubic millimeter, and segmented cells, 78 per cent.

Studies of blood chemistry showed a sugar content of 130 mg. per hundred cubic centimeters, serum protein content of 7 per cent and icterus index of 15 per cent. The urine was amber colored, with a specific gravity of 1.026. There were many pus cells and an occasional red blood cell.

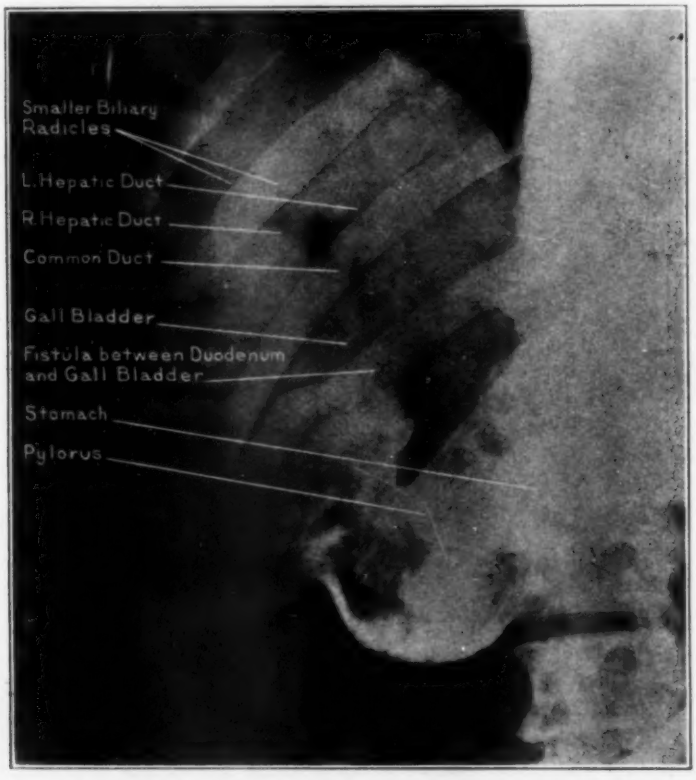

Fig. 2.—Following a meal of barium sulfate, a roentgenogram of the stomach, gallbladder and liver region revealed a barium fleck independent of the stream of barium sulfate about the second portion of the duodenum, which was interpreted as a fistulous opening between the gallbladder and duodenum, and air was seen in the extrahepatic biliary ducts and biliary radicles.

The patient was hospitalized and treated symptomatically, and an attempt was made to bring his diabetes under control. On about the sixth day, one of us (D. C. D.) was called into consultation. Flat roentgenograms of the abdomen were taken following instillation of dye into the gallbladder. A series of roentgenograms of the gastrointestinal tract and studies after a barium sulfate enema were made. A roentgenogram of the gallbladder failed to visualize a gallbladder

shadow, but there was a shadow representing a dilatation of the common and hepatic ducts. This shadow extended into the hepatic area as a branched shadow representing the larger and smaller bile radicles. The colon was dilated; otherwise it was normal. The fluoroscopic examination of the stomach and duodenum, including flat roentgenograms, showed that they were normal except that on fluoroscopic examination a barium speck, separated from the stream of barium sulfate, was seen in the upper wall of the second portion of the duodenum. It

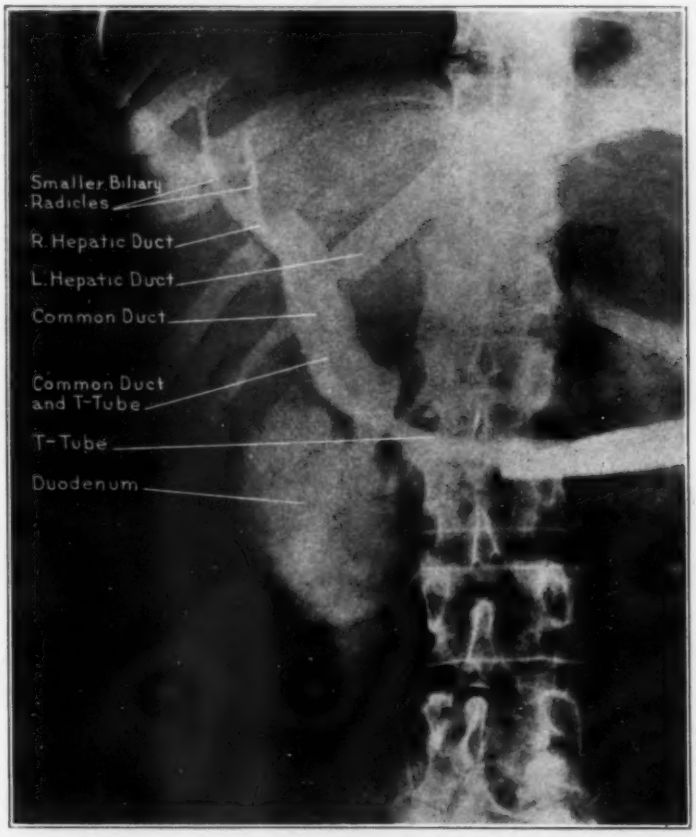

Fig. 3.—A roentgenogram made six weeks following operation. A 10 per cent solution of sodium iodide was injected into the T tube; the opaque material is seen to fill the common and hepatic ducts and liver radicles and to enter into the lumen of the bowel.

could not be dislodged from its bed by external manipulation of the abdomen. This was thought to be an opening of the fistula into the bowel.

OPERATION

With the patient under spinal anesthesia supplemented with cyclopropane, the abdomen was opened through an incision in the right upper rectus. The stomach and pylorus were free of pathologic changes. The greater portion of the duodenum was found firmly adherent to the right lobe of the liver. Due to the density of

the adhesions, much effort and time were spent in releasing the bowel from the liver. The gallbladder was found to be small and fibrotic and free of stones and its fundus firmly adherent to the duodenum. On release of the gallbladder from the bowel, an opening, or communication, between the two organs was seen. The fistulous opening in either organ did not exceed 3 mm. in diameter. The opening in the bowel was closed by first enlarging the fistulous opening in the bowel to obtain good exposure. It was then closed in a transverse manner, O chromic enterostomy suture being used for the mucous coat. Similar suture for the mus-

Fig. 4.—Flat roentgenogram of the upper part of the abdomen made approximately eight months following operation, after the patient was well and had returned to work, shows a normal outline of the liver and no dilatation of the extrahepatic ducts or biliary radicles.

cular and serous coats and the suture line was reenforced with interrupted cotton suture. The gallbladder contained much necrotic material. The cystic duct was patent, and the common duct was dilated to several times its normal size. Its walls were thickened and tense from intraluminal pressure, and, on aspiration of the common duct, approximately 10 to 15 cc. of air or gas was withdrawn before the light-colored bile fluid, mixed with flakes of debris, appeared in the

syringe. The common duct was opened for a distance of 3 to 4 cm. under guidance of stay sutures of cotton placed in either side of the wall of the duct, at such points to permit good exposure when opened. On incision of the duct, an additional amount of gas and air, with debris, escaped. Further exploration of the duct revealed a large amount of sandstone in its lower end. This was removed with a scoop and followed by irrigation of the duct with isotonic solution of sodium chloride. The upper end of the common and hepatic ducts was free of stone pigment. The patency of the common duct was established by passing a medium-sized probe through the ampulla and sphincter of Oddi into the bowel. A T tube was placed in the common duct, and its long flange end was permitted to escape through the sphincter of Oddi into the lumen of the bowel. The opening of the common duct was then closed with interrupted chromic surgical gut suture to the level where the tube made its escape, and the gallbladder and cystic duct were removed. All raw surfaces opposite the common duct and bed of the gallbladder were closed with running OO plain surgical gut suture. A Penrose drain was placed in the gallbladder fossae, and this was allowed to emerge from the abdomen through a counteropening in the lateral wall of the abdomen. The T tube was brought through the upper angle of the incision, with closure of the wound by the layer method.

The patient's surgical convalescence was an uninterrupted one. His low nutritional status was cared for by multiple blood transfusions and parenteral administration of amino acids. The Penrose drain was removed by the eighth day, having been shortened on alternate occasions. The T tube was worn for three months following the operation.

Culture of the aspirated bile from the common duct revealed growth of Bacillus coli and Bacillus proteus after twenty-four hours' incubation.

CONCLUSION

1. The physiologic and pathologic features of spontaneous internal biliary fistula have been discussed.

2. Review of the literature shows that due consideration has not been given the clinical picture and the importance of evaluation of the different biliary antecedents as a diagnostic aid in internal biliary fistula, but, instead, more attention has been directed to the roentgenologic findings for diagnosis.

3. Because of early fibrosis and contraction of the fistula, only in a small per cent of internal biliary fistulas will roentgenograms alone show the fistula.

4. To increase the percentage of diagnosis commensurable with the number of fistulas found at the operating table, we suggest that in addition to roentgen studies more attention be given to the clinical picture.

5. Early diagnosis based on the presumptive signs and roentgenologic studies and maintenance of a good surgical program are the best means of combating the problems of internal biliary fistula.

6. The points of interest in the case reported are the preoperative findings, clinical picture and visualization of air in bile passages and cure of the fistula.

ARREST OF GROWTH OF THE EPIPHYSES

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AND
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GRAND RAPIDS, MICH.

ARREST of epiphysiodiaphysial growth, or epiphyseodesis, was originally described by Phemister [1] in January 1933, having been proposed as a method of obtaining equalization of leg length in growing children. This procedure involves the removal of a block of bone 3 cm. in length and 1.5 cm. in width from across the epiphysial line. This block is about 0.5 cm. deep. After removal of the block of bone the epiphysial line is curetted for a distance of 2 to 5 cm. lateralward and about 10 to 15 mm. in depth. It is the experience of Hatcher that stripping of the periphery of the epiphysial line is sufficient and that deep curettement is unnecessary. The block of bone is then turned end on end and reinserted, so that a bony bridge covers the epiphysial line (fig. 1 *B*).

There have naturally arisen modifications of the original technic. Philip Wilson [2] went a step farther in cauterizing the epiphysial line after curettement. J. Warren White [3] devised a hollow, square chisel, ½ inch (1.2 cm.) on a side, which he taped through the epiphysial line diagonally, so that two corners cut through the line and two corners cut on either side of the line (one distally and one proximally). The chisel cuts ¾ inch (2 cm.) deep. After removal of the block, the adjacent portions of the epiphysial line are thoroughly curetted. The chisel is then rotated 90 degrees and reinserted and the block taped into place by means of a loosely fitting obturator in the shaft of the instrument. This results in a bony bridge across the epiphysial line (fig. 1 *A*). Haas [4] reported the use of rustless steel wire looped about

From the Orthopedic Service of Blodgett Memorial Hospital.

1. Phemister, D. B.: Operative Treatment of Longitudinal Growth of Bones in the Treatment of Deformities, J. Bone & Joint Surg. **15**:1 (Jan.) 1933.

2. Wilson, P. D., and Thompson, T. C.: A Clinical Consideration of the Methods of Equalizing Leg Length, Ann. Surg. **110**:992 (Dec.) 1939.

3. White, J. W., and Stubbins, S. G., Jr.: Growth Arrests for Equalizing Leg Lengths, J. A. M. A. **126**:1146 (Dec. 30) 1944. White, J. W.: A Practical Graphic Method of Recording Leg Length Discrepancy, South. Med. J. **33**:946 (Sept.) 1940. White, J. W., and Warner, W. P., Jr.: Experiences with Metaphyseal Growth Arrests, ibid. **31**:411 (April) 1933.

4. Haas, S. L.: Retardation of Bone Growth by a Wire Loop, J. Bone & Joint Surg. **28**:25 (Jan.) 1945.

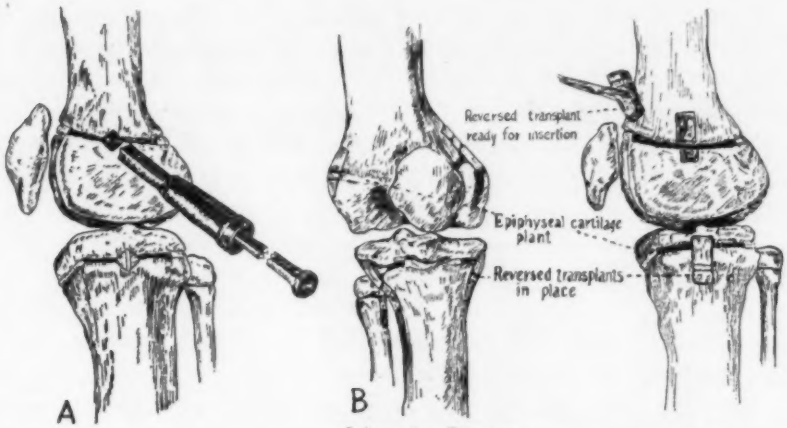

Fig. 1.—*A*, White's technic, demonstrating the rectangular block and 90 degrees of rotation plus curettement. Note the hollow obturator employed, the operator tapping the block of bone into its bed. *B*, Phemister's technic of curettement and reversal block method (Campbell, W.: Operative Orthopedics, St. Louis, C. V. Mosby Company, 1939).

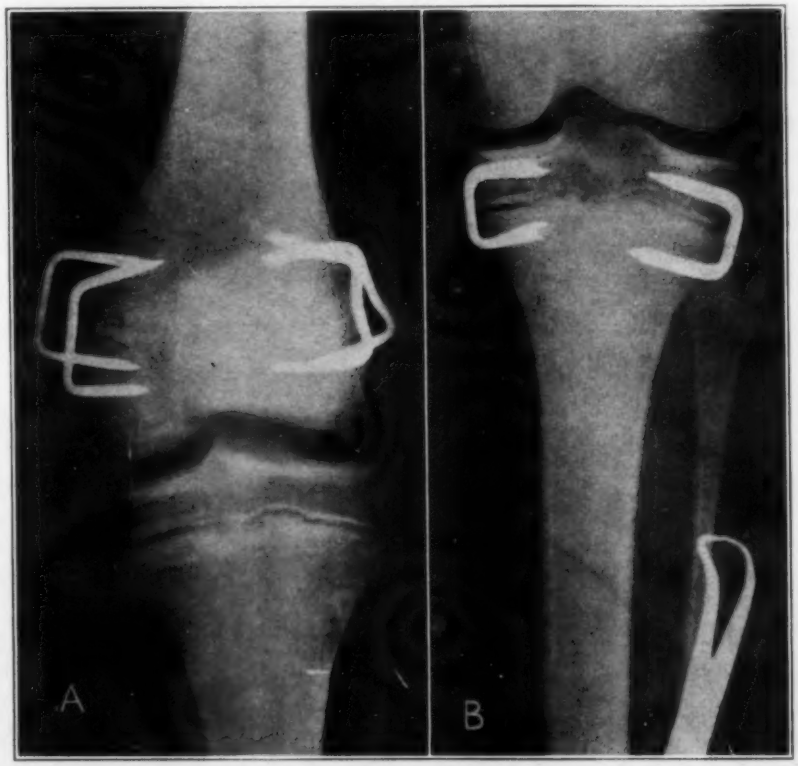

Fig. 2.—*A*, staples across the lower part of the femoral epiphysis. *B*, staples across the upper part of the tibial epiphysial line. (Courtesy of Dr. Walter P. Blount.)

the distal femoral epiphysis to slow growth. He successfully retarded growth in length without destroying the epiphysis. The wire may be removed when the desired result has been obtained. Blount [5] recently developed a technic utilizing the rational of Haas's wire loop. He simplified the true retardation process, without epiphysial destruction, by employing staples of stainless steel similar to those of R. E. Burns

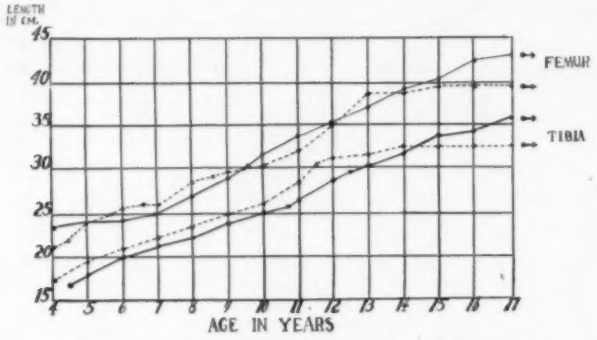

Fig. 3.—Growth increment curve of Hatcher.

(fig. 2). To date, all indications seem to prove that the method is efficient in arresting growth.

CALCULATION

The most difficult and yet the most important phase of this operation is determining the time for operation and in which epiphysis or epiphyses growth is to be arrested.

TABLE 1.—*Average Normal Figures for Growth Expectancy of the Lower Extremities*

Age	Male		Female	
	Cm.	Inch	Cm.	Inch
7	28.88	11.55	21.05	8.42
8	26.47	10.58	18.39	7.35
9	23.26	9.3	16.02	6.4
10	20.14	8.06	12.16	4.86
11	17.07	6.82	8.37	3.34
12	14.34	5.73	6.40	2.56
13	10.70	4.28	3.51	1.6
14	7.27	2.9	1.80	0.72
15	4.24	1.7	0.52	0.2—
16	2.09	0.83	0.14	

A complete knowledge of skeletal growth and maturity in children has not as yet been reached, and there are factors over which the surgeon has no control. However, over a period of years, growth expectancy tables (table 1), developmental curve graphs (fig. 3) and clinical records have given the clinician guides with which to work.

5. Blount, W. P.: Personal communication to the authors.

Still, probably many surgeons are reluctant to embark on this operation because of the mathematical variations and, in some minds, uncertainty of results. It is realized that these growth expectancy curves and length of bones of lower extremities, as recorded by Baldwin [6] and Hatcher, Meredith and Gill and Abbott,[7] are averages, but they are working scales and the results obtained by consulting them in calculations are good. The surgeon naturally wishes a perfect result, but he is not seeking mathematical accuracy in equalizing limbs. Rather, he seeks a noticeable improvement in limb length that need not be 100 per cent perfect in measurement to be labeled a good clinical result.

A constant factor in the growth of the lower extremity is the contribution of each of the epiphyses: upper femoral, 12 per cent; lower femoral, 40 per cent; upper tibial, 27 per cent, and lower tibial 21 per cent. These figures may vary in chondrodysplasia.

It has been determined that girls do not grow after menstruation has begun and that they mature earlier than boys. Generally speaking, arrest of growth of the lower femoral epiphysis will retard growth of the limb ⅜ inch (0.9 cm.) per year, and arrest of growth of the proximal tibial epiphysis retards growth of the limb ¼ inch (0.6 cm.) per year. Wilson [8] considers boys to stop growth at 16 years and girls at 14 years, and one finds in checking growth increment curves (fig. 3) that the increase in length of long bones tapers off to the horizontal at these ages.

In view of the variable factors involved in predictions of growth and in an endeavor to minimize these inaccuracies, every child who is a candidate for arrest of epiphysial growth should have an evaluation of skeletal maturation. This is accomplished by a roentgenogram of the carpal development, as scaled by Todd.[9] If the chronologic age varies six months or more, the bone maturation age is used in the calculations. We have seen variations in bone age and chronologic age of one year in youngsters of approximately normal weight, height and sexual development for their chronologic age.

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6. Baldwin, B. T.: Physical Growth of Children from Birth to Maturity, in Studies in Child Welfare, Iowa City, University of Iowa, 1921, vol. 1, no. 1.

7. Gill, G. G.: The Cause of Discrepancy in Length of the Limbs Following Tuberculosis of the Hip in Children: Arrest of Growth from Premature Closure of the Epiphyseal Cartilages About the Knee, J. Bone & Joint Surg. **26**:272 (April) 1944; A Simple Roentgenographic Method for the Measurement of Bone Length: A Modification of Milliwee's Method of Slit Scanography, ibid. **27**:767 (Oct.) 1944. Gill, G. G., and Abbott, L. C.: Practical Method of Predicting Growth of the Femur and Tibia in the Child, Arch. Surg. **45**:286 (Aug.) 1942.

8. Straub, L. R.; Thompson, T. C., and Wilson, P. D.: The Result of Epiphyseodesis and Femoral Shortening in Relation to Equalization of Limb Length, J. Bone & Joint Surg. **27**:254 (April) 1945.

9. Todd, T. N.: Atlas of Skeletal Maturation (Hand), St. Louis, C. V. Mosby Company, 1937.

MEASUREMENT

The universal method of measuring leg length is probably straight line mensuration by metal tape from the anterior-superior spine of the ilium to the medial malleolus at the ankle. This procedure is often checked when discrepancy in leg length exists by block lifts placed under the short limb, leveling the pelvis to the horizontal plane. These two methods are purely clinical and are subject to the error of personal equations. Two examiners will often vary slightly in their measurements, both of limb length and of discrepancy of length.

Roentgenologic examination has been used to measure more accurately lengths of the long bones. By employment of a series of teleroentgenograms, actual progress in growth is recorded and preserved. Phemister's [1] original article included measurements of the diaphyses of the bones involved by teleroentgenographic examination of the entire lower extremity.

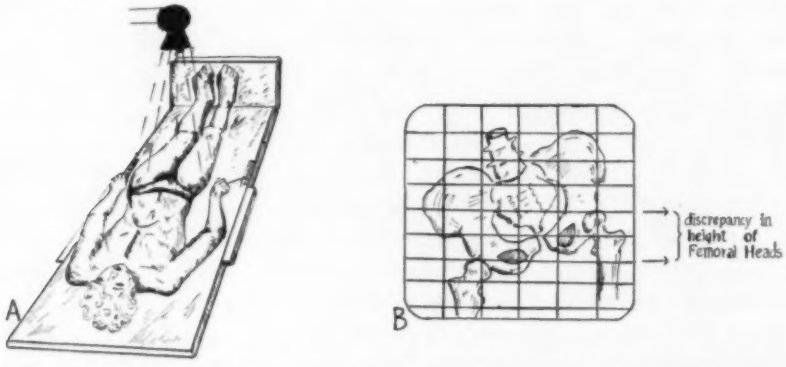

Fig. 4.—*A*, recording discrepancy in leg length by pelvic tilt and height of the femoral heads (after J. W. White). *B*, drawing of roentgenogram, with shadow of wires in casette.

It is possible, therefore, to utilize roentgenologic examination in recording limb length and discrepancy as a check on purely clinical mensuration. Two practical methods have been developed. J. Warren White [3] records discrepancy only, by taking a flat roentgenogram of the pelvis. The patient is placed on the x-ray table and, by means of straps attached to the sides, pulls himself firmly against the foot plate, so that the two feet exert equal pressure (fig. 4). A flat roentgenogram is taken, a Bucky diaphragm being employed with the tube at the usual distance. The exertion of pressure by the short leg will cause a compensatory tilt in the pelvis and will be recorded on the plate. Originally, White determined the discrepancy by drawing tangents to the femoral heads and measuring with a celluloid triangle. This has been modified by placing horizontal and vertical wires in the cassette. Distortion will be present, as the cassette is some 2 inches (5 cm.)

below the table top and the femoral heads are 3 inches (7.6 cm.) above. This is a 5 inch (12.7 cm.) total. Ordinarily, the tube-cassette distance is 30 inches (76.2 cm.), giving 20 per cent magnification. The markers in the cassette tend to cancel out discrepancies, as the markers remain constant. A simple modification of this procedure can be pursued under fluoroscopic examination. With the patient exerting pressure on both feet, blocks of known thickness are placed under the foot of the short side, leveling the pelvis. This leveling is checked by horizontal wires in the fluoroscopic field. No correction need be made; the total block thickness is recorded on the patient's chart.

Gill [7] has modified Milliwee's method of slit scanography to obtain actual roentgenologic records of the length of the long bone. The tube moves from the hip distalward at the rate of 36 inches (91 cm.) per ten seconds by means of a rope and pulley attached to a weight. The quality of the roentgenogram is best with the tube distance at 30 inches. Error of distortion is not more than 2 per cent.

It is of importance to call attention to the fact that children under 8 years of age with excessive shortening due to tuberculosis of the hip or old septic arthritis need careful study. Gill has shown that premature closure of the epiphyses about the knee occurs in such cases. A child falling in this category should have the epiphyses about the knee of the involved side studied by roentgenographic examination. Characteristic contours reveal premature fusion. We believe that one of our earlier patients operated on fell into this group. Little change in discrepancy results after five years. We feel now that the epiphyses about the knee of the short leg, from which we expected future growth, had prematurely fused prior to the time of the arrest of the epiphysial growth on the normal side.

The method usually employed to determine which epiphysis to obliterate is based on the percentage of length now lacking on the short side in relation to the total expected growth of the limb. A simple formula is: $\frac{\text{Shortening present}}{\text{Expected growth}} = \%$ of growth to eliminate.

A clinical example follows: A boy 10 years of age has 2 inches of shortening in the left leg. The problems of calculation are three: What is his expected growth? What per cent of growth is to be eliminated on the normal side? What epiphysis is to be obliterated? Consulting the table of growth expectancy, one finds that a boy of 10 years expects 20.14 cm. (8.06 inches) of growth before his maturity is reached. The formula now resolves itself into figures: $\frac{2.00}{8.06} = 25$ per cent. It is revealed that to expect equalization of the legs at maturity 25 per cent of the growth of the normal side should be obliterated. The upper tibial epiphysis contributes 27 per cent to the growth of the leg. This is the closest value to the calculated figure. In these circumstances, arrest of the proximal tibial epiphysis will gain

the desired result. By postponing the operation until the patient has reached 10½ years, one finds the expectancy to be 18.61 cm. (7.40 inches). Thus, $\frac{2.00}{7.40} = 27.1$ per cent of growth to be obliterated—a closer estimation—and is satisfactorily accomplished by operation on the proximal tibial epiphysis.

During the earlier years of this operation, errors on the conservative side have been prevalent; the surgical operation having been performed too late resulted in a permanent discrepancy after maturity. The ages of 10 to 12 years seem to be optimum for epiphysial fusion in cases in which 2 inches of shortening exists; double fusion at 12 years (distal femoral and proximal tibial) will bring approximal equalization of legs at 16 years of age.

TECHNIC

Surgical technic must be painstaking and solid union of turned blocks insured. A dry field for clear visualization of the epiphysial line is essential and is obtained by employing a pneumatic tourniquet at 6 to 8 pounds' (2.7 to 3.6 Kg.) pressure. An Esmarch bandage was used only on the first few patients. Elevation of the extremity to an almost vertical position during preparation of the skin suffices. The tourniquet is pumped to required pressure immediately after preparation of the skin, and the limb is lowered to the operating table for draping. Beginning laterally, one notices that the fascia lata is taut in extension; slight flexion of the knee will release tension and facilitate retraction for better visualization of the distal femoral epiphysial line. Care must be exercised in cutting the block outline through cortical bone. A sharp osteotome of ½ inch (1.2 cm.) is used, being angled into the cortex to prevent splintering, especially in the transverse cuts. It is important that the rotated end and refitted cortical block fit snugly to insure fusion. It can be gently impacted by blows with a small-headed mallet. After curettement and reinsertion of the block of bone in the lateral aspect, the medical aspect is exposed and the technic repeated. Obviously, a team of two operators reduces the time element in operating on medial and lateral aspects simultaneously. The approach to the upper fibular epiphysis and lateral aspect of the upper tibial epiphysis is slightly more difficult technically. Caution in exposure is necessary to prevent injury to the peroneal nerve. At least a 4 inch (10 cm.) incision is necessary. If the dissection is carried along the medial anterior border of the biceps femoris tendon, the periosteum being retracted outward and away from the fibular head, the peroneal nerve follows in the soft tissues and is lateral to the fibular head and field of operation. The fibular epiphysis can be excised. The wound is closed in layers and a pressure bandage applied over sterile dressings. Sterile sheets of cotton batting bound snugly with elastic bandage

suffice. Warren White immobilizes the limb in a plaster from groin to ankle for a period of three weeks. Others, however, employ no plaster dressing, allowing patients up in seven to ten days. Our practice has been to allow patients to dangle their legs over the bed when stitches are removed and to use crutches in ten days.

Blount's staples are made from 3/32 inch (0.2 cm.) rods of chrome nickel stainless steel. The limbs are ¾ inch (1.9 cm.) and the cross member ½ inch (1.2 cm.). Exposure of the epiphysis is essentially the

Fig. 5.—The clinical deformity.

same as described in the aforementioned technic. Two staples are introduced on a side, ½ inch apart. It is unwise to allow the metal to straddle any structures of soft tissue other than periosteum. Blount stated that it is better to bury the staple under periosteum, thereby assuring firm fixation and lessening the possibility of loosening and gradual working out. Roentgenologic control is utilized throughout the operation. After closure of the incisions, a long plaster of paris cast is applied to the leg, including the foot, and remains on for three weeks. Walking is permitted as soon as the patient wishes.

The closure of the epiphysis is checked by roentgenograms three to six months postoperatively. This will warn of nonclosure and develop-

Fig. 6.—A roentgenogram of the patient in figure 5 revealed asymmetric fusion of the lower femoral epiphysis and relative overgrowth of the medial femoral condyle.

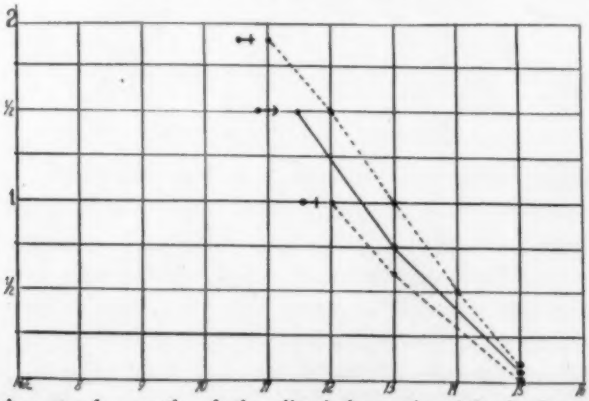

Fig. 7.—Arrest of growth of the distal femoral epiphysis for shortening in residual anterior poliomyelitis. Age at operation and discrepancy, with gradual equalization over a four year period.

ment of deformity, which may be prevented by a second operation. As a rule, deformity will appear in eighteen months. Asymmetric fusion results in deformity about the knee. Cases of genu recurvatum, varus and valgus have occurred. In 1 of the patients in this group a knock knee developed (later corrected by osteotomy) (figs. 5 and 6). To date we have not seen the side operated on shorter at maturity than the originally involved extremity.

RESULTS

Results naturally cannot be evaluated until the subjects reach or closely approximate skeletal maturity. Clinical measurement of the legs is a satisfactory method for all practical purposes. Lift blocks

TABLE 2.—*Analysis of Twenty-One Cases in Which Operation Was Done by Phemister's Method*

Case	Age, Yr.	Sex	Short, In.	Final Short, In.	Operation	Correction, %
E. B.	13	F	2.0	1.5	Lower femoral epiphysis	25
E. R.	10	M	1.75	1.0	Upper tibial epiphysis	40
L. D.	9.6	M	2.25	0.5	Upper tibial epiphysis	80
I. S.	12	F	1.0	0.0	Lower femoral epiphysis	100
E. B.	13	F	2.0	0.75	Lower femoral epiphysis and upper tibial epiphysis	64
D. P.	14	M	2.25	1.00	Lower femoral epiphysis and upper tibial epiphysis	60
O. R.	12	M	2.50	0.0	Lower femoral epiphysis	100
B. L.	8.5	F	1.75	0.5	Upper tibial epiphysis	80
B. L.	11	F	1.75	0.0	Upper tibial epiphysis	100
L. T.	11.5	M	1.75	0.0	Upper tibial epiphysis	100
H. H.	11.5	M	1.50	0.0	Lower femoral epiphysis	100
A. S.	13	F	1,25	0.75	Lower femoral epiphysis	40
J. V.	11.5	F	2.0	1.0	Upper tibial epiphysis	50
G. K.	12.5	M	1.25	0.25	Upper tibial epihpysis	80
J. S.	11	F	1.50	1.0	Lower femoral epiphysis	33
D. K.	9	M	4.00	1.75	Lower femoral epiphysis	57
R. D.	10.5	M	2.50	0.75	Upper tibial epiphysis	66
E. C.	13	M	3.0	1.0	Upper and lower tibial epiphysis and lower femoral epiphysis	66
W. G.	12	M	1.50	0.5	Lower tibial epiphysis	80
B. W.	13	F	1.0	0.0	Lower femoral epiphysis	100
F. R.	11	M	2.75	2.0	Upper tibial epiphysis	29

under the short side, leveling the pelvis, also afford a good clinical check. White's method or fluoroscopic check is more accurate and affords a permanent record of progress toward equalization of the limbs.

What is a "good" result? Clinical evaluation varies in different cases (fig. 7). A child with a 4 inch (10 cm.) discrepancy ending his extremity growth with ¾ to 1 inch (1.9 to 2.5 cm.) shortening may be considered a good result. However, a 2 inch (5 cm.) discrepancy ending with 1 inch (2.5 cm.) shortening would seem only fair. Percentage of gain on the discrepancy may arbitrarily divide the results. A 75 per cent or more gain is a good result, 25 up to 75 per cent mediocre and less than 25 per cent poor.

Analysis of cases of 21 patients operated on after the method of Phemister, now at or near skeletal maturity, reveals the following figures:

	Patients, %
Good result (75 to 100% gain)	48
Fair result (25 to 75% gain)	47
Poor result (0 to 25 % gain)	5

The shortening was due to residual anterior poliomyelitis in 15 cases, old septic arthritis of the hip in 2 cases, old tuberculosis of the hip in 1 case and congenital or idiopathic shortening in 3 cases. It is to be noted that in 2 instances a double arrest was performed and in 1 instance a triple arrest.

COMMENT

End results will improve with increase in experience. Reluctance to operate at an early age should give way to energetic handling of the problem (average age at operation in this series is 11 years and 4 months). If anything, we have erred on the conservative side. The employment of evaluations of bone age and roentgenologic examination in recording discrepancy in leg length will aid in eliminating inaccuracies.

It is evident that arrest of epiphysial growth, despite the fact that it is an irreversible operation, should take its place with foot stabilization, tendon transference and bone grafting. The recent development of arresting staples by Blount has been a definite forward step in both preserving the life of the epiphysis and temporarily arresting growth. Further investigation of this technic after removal of the staples is aimed at answering two important questions: Will growth be resumed at the same rate as at the opposite epiphysis, and will growth continue as long as on the other side? The operation of arrest of growth of the epiphyses is another surgical aid to be employed in growing children for the correction of discrepancies in leg length due to congenital conditions, tumors, the results of trauma and the residuum of infectious diseases.

SPONDYLOLISTHESIS

Additional Variations in Anomalies in the Pars Interarticularis

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ALONG with the accelerated tempo in investigations of syndromes of the lower part of the back during recent years, prespondylolisthesis and spondylolisthesis have been uncovered as relatively frequent findings. With reference to the defect in the neural arch, there has been speculation as to whether it has resulted from an intrauterine disturbance sufficient to fracture or to impede circulation to the isthmic portion, with the resultant defect of a pseudarthrosis, or whether there has been a developmental failure of bony fusion of the two separate ossification centers of this portion of the neural arch. We are prone to support the latter view and feel that other congenital anomalies of this isthmic portion may be present in addition. We seek to demonstrate some of these in the following presentation.

The defect in the neural arch referred to as spondylolysis or spondyloschisis involves the isthmic portion, or pars interarticularis, situated between the superior and inferior articulating facets. In the "preslipping stage" and in the stage of actual forward dislocation of the vertebral body, the defect may involve only one side of the neural arch or both sides. When the defect involves only one side of the neural arch in a case of actual forward displacement of the vertebral body, a mechanical problem is posed. Moored as it is to the intact side of the neural arch, as demonstrated by posterior oblique roentgenograms, how can the vertebral body assume a position of forward dislocation, as demonstrated by lateral roentgenograms? If this were effected by rotation, both the lateral and the anteroposterior roentgenograms would demonstrate this. As will be seen later, they do not. The forward displacement in the face of one intact side must be explained on the basis of additional congenital anomalies.

In order clearly to demonstrate the variations in anomalies involving these particular lesions, the following types of cases will be presented: (1) defects in both sides of the neural arch without forward displacement of the vertebral body ("preslipping stage"); (2) defects in both

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sides of the neural arch with forward displacement of the vertebral body (spondylolisthesis); (3) defect in only one side of the neural arch without forward displacement of the the body ("preslipping stage"); (4) defect in only one side of the neural arch with forward displacement of the vertebral body (spondylolisthesis), and (5) reversed spondylolisthesis.

I. DEFECTS IN BOTH SIDES OF THE NEURAL ARCH WITHOUT FORWARD DISPLACEMENT OF THE VERTEBRAL BODY

Bilateral laminar defects without displacement constitute the entity described as the "preslipping stage," or prespondylolisthesis. The defects are easily demonstrated but the laminas are of sufficient integrity to maintain continuity of the neural arch and proper (normal) alinement of the related vertebral bodies. In this situation, clinical symptoms could be ascribed only to the fact that bony defects, although "intact," indicate the presence of associated defects of soft tissue and ligamentary defects and therefore a high degree of vulnerability of this particular part of the spine to strain forces. The imposition of severe enough trauma on this abnormal complex could disrupt its continuity completely, and the vertebra, freed from its moorings, would be displaced forward in proportion to the disruption force.

II. DEFECTS IN BOTH SIDES OF THE NEURAL ARCH WITH FORWARD DISPLACEMENT OF THE VERTEBRAL BODY

The complex seen in roentgenograms in a typical case is a forward displacement of the body in the lateral projection and a defect of the pars interarticularis on both sides in the right and left posterior oblique projections. The neural arch has been dissolved so far as normal mechanics are concerned, and the vertebral body, adrift, has moved under the descending weight of the spinal vertebrae, into a forward displacement. Findings on physical examination include the appearance of a shortening of the trunk, as though it had settled into the pelvis, prominence of the hips and a palpable, locally tender "step-off" in the alinement of the spinous processes as one's finger progresses over the sacrum upward along the midline of the back. These findings are in proportion to the extent of the anterior dislocation of the body. While the lateral roentgenographic projections later may disclose an increased lordosis of the lumbar portion of the spine, usually the lower part of the back on physical examination presents a rather flat appearance, understandable on the basis of the paravertebral muscles having become more superficially prominent as they are lifted up over the prominent sacrum. The masked lordosis is better appreciated on palpation in the midline upward from the "step-off." These conditions may or may not be clinically active. The causes of these phases of decompensation are varied: further displacement from trauma, general physical debility of a tem-

porary phase, transient myositis from strain and similar factors. This type most frequently requires spinal fusion. Case 1 illustrates a typical case.

CASE 1.—R. C. E. is a 25 year old white man giving a history of several injuries to the back prior to admission and presenting physical findings characteristic of the lesion. Conservative therapy has not allayed his symptoms, and he will undoubtedly require spinal fusion. In figure 1 *A* the anteroposterior projection discloses no visible defect in the neural arch. The lateral projection (fig. 1 *B*) shows the forward displacement of the fifth lumbar vertebra on the sacrum. The right posterior oblique projection (fig. 2 *A*) shows an absence of the right pars interarticularis, constituting a defect in the continuity of the neural arch. The

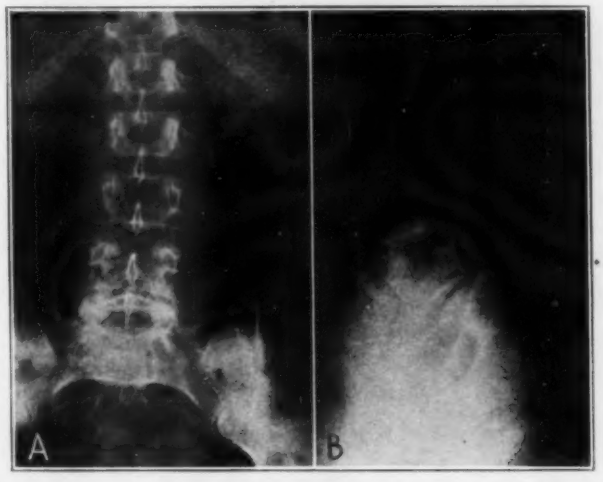

Fig. 1 (case 1).—*A*, anteroposterior projection. Slight condensation of bone is present about both lumbosacral joints. There is no visible defect in the neural arch. *B*, lateral projection. There is a 1 cm. anterior displacement of the body of the fifth lumbar vertebra, with moderate lipping of the anterior corner of the sacrum.

left posterior oblique projection (fig. 2 *B*) shows the left pars interarticularis to be present, but there is a defect near the base of the inferior articular facet. There is, in this instance, a bilateral spondyloschisis and spondylolisthesis, the former characterized by an absence of the pars interarticularis on one side and a failure of fusion with the lamina on the other side.

III. DEFECT IN ONLY ONE SIDE OF THE NEURAL ARCH WITHOUT FORWARD DISPLACEMENT OF THE BODY

A unilateral laminar defect in the neural arch without displacement of the vertebral body is understandable. On one side, as viewed in the posterior oblique projection, there is a spondyloschisis. On the other, the pars interarticularis is of normal proportions and integrity. There could be no means of forward displacement unless in a limited way by rotation. The lateral projection in these cases shows a normal alinement of the involved body. Case 2 is an illustration of such a lesion.

CASE 2.—H. C. H. is a 40 year old white man who was admitted to the hospital with the complaint of pain in multiple joints, including the lower part of the back. On the basis of roentgenographic findings, he was sent to us as having a deformity of the lower part of the spine. Foci of infection were searched for, and after tonsillectomy he experienced definite improvement of all joints, including the lumbosacral region. The physical examination of his back on discharge was noncontributory. In figure 3 the anteroposterior projection (*A*) discloses an incomplete fusion of the lamina of the fifth lumbar vertebra at the base of the spinous process. The lateral projection (*B*) shows no anterior displacement of the body of the fifth lumbar vertebra. In the right posterior oblique projection

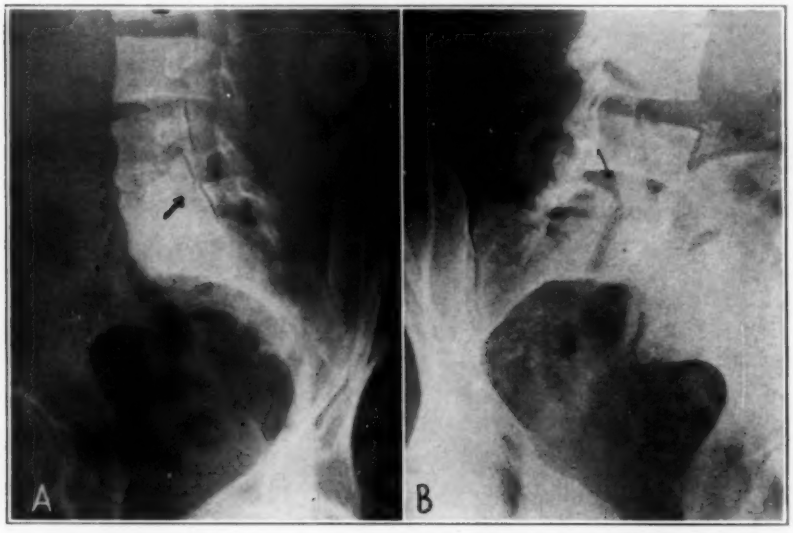

Fig. 2 (case 1).—*A*, right posterior oblique projection. There is absence of the right pars interarticularis, showing the unbroken line of the cephalad surface of the lamina extending backward from the inferior articular facet. There is downward displacement of the superior articulation of the fifth lumbar vertebra, so that it nearly impinges on the inferior articulation. *B*, left posterior oblique projection. The left pars interarticularis is present but shows a 2 mm. defect near the base of the inferior articular facet. Note that the line of the cephalad surface of the lamina is broken by the shadow of the pars interarticularis. In these and all subsequent illustrations, the arrow points to the region of the pars interarticularis of the fifth lumbar neural arch.

(*C*) the pars interarticularis appears well formed and solidly continuous throughout. The left posterior oblique projection (*D*) shows the left lamina to be less than one third the width of the right and to have no bony continuity with the superior articular facet. The left pars interarticularis is completely absent. This case, then, presents a unilateral defect not from failure of fusion of the pars interarticularis with the lamina but from a congenital absence of the former, unattended by any forward displacement of the vertebra—a unilateral spondyloschisis without spondylolisthesis.

IV. DEFECT IN ONLY ONE SIDE OF THE NEURAL ARCH WITH FORWARD DISPLACEMENT OF THE VERTEBRAL BODY

In some instances there is a unilateral defect in continuity with forward displacement of the vertebral body. The oblique projections again show a spondyloschisis on one side and an intact pars interarticularis on

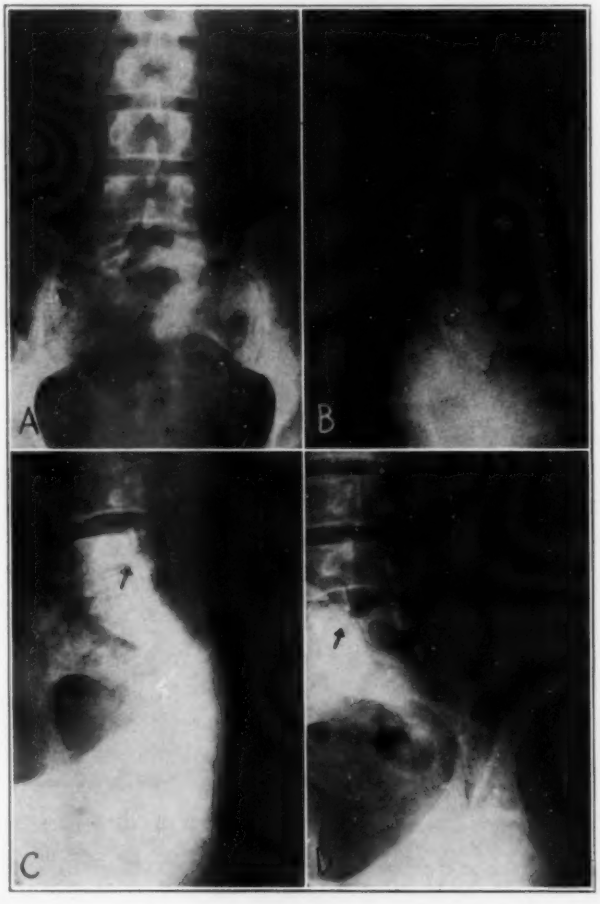

Fig. 3 (case 2).—*A*, anteroposterior projection. This view shows only an incomplete fusion of the laminas on the fifth lumbar space at the base of the spinous process. *B*, lateral projection. There is no anterior displacement of the body of the fifth lumbar space. *C*, right posterior oblique projection. This view shows the right half of the neural arch in profile. The pars interarticularis of the right lamina is shown to be well formed and solid throughout. *D*, left posterior oblique projection. This view shows the left lamina to be less than one third the width of the right one and to have no bony connection with the superior articular facet; in other words, the pars interarticularis is absent. The cephalad surface of the lamina forms a smooth, unbroken, horizontal line of cortical bone from the spinous process to the superior surface of the inferior articular facet, giving an appearance entirely different from the normal laminar outline on the right, where the cephalad surface of the lamina curves upward to the inferior surface of the superior articular facet.

the opposite side. There is no evidence of lateral bending or rotation, since the articular facets bear a normal relationship one to the other. What, then, is the mechanism allowing for the dislocation? Case 3 is an illustration of such a lesion.

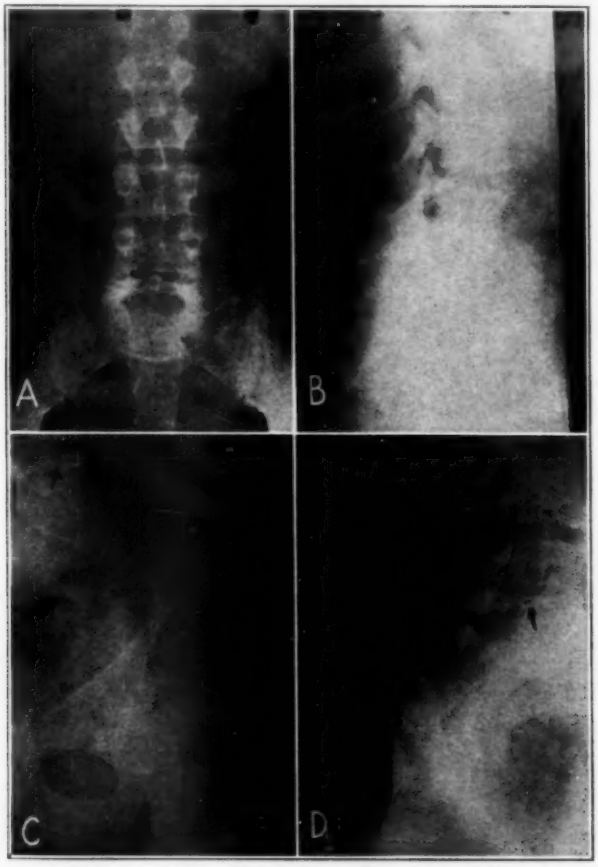

Fig. 4 (case 3).—*A*, anteroposterior projection. It is not remarkable. *B*, lateral projection. There is a 1 cm. anterior dislocation of the body of the fifth lumbar vertebra on the sacrum, with narrowing of the fifth lumbar disk by one half. Slight lipping of the anterior margin of the first sacral segment is present. *C*, right posterior oblique projection. The pars interarticularis of the right lamina is intact throughout (this is confirmed by stereoscopic views) but is unusually long and horizontal in position. *D*, left posterior oblique projection. The left pars interarticularis of the fifth lumbar space shows a definite defect of continuity near its midpoint, but the apparent separation of the parts is less than 2 mm. On this side also, the pars interarticularis is unusually long and horizontally placed.

Case 3.—J. B. L. is a 34 year old white man who sustained an injury overseas when he fell from a dock, striking his left side against a crane. His immediate symptom was pain along the right costal margin, and, when, several days later, he complained of mild pain in the lower part of the back, roentgenograms were made and the spondylolisthesis was seen in the lateral view. He was admitted to the hospital on the basis of these roentgenologic findings and subsequently

returned to the mainland. On arrival, he stated that he was completely free from pain low in the back. Except for a prominence of the sacrum and an increased lordosis discernible on deep palpation along the spinous processes, physical examination was noncontributory.

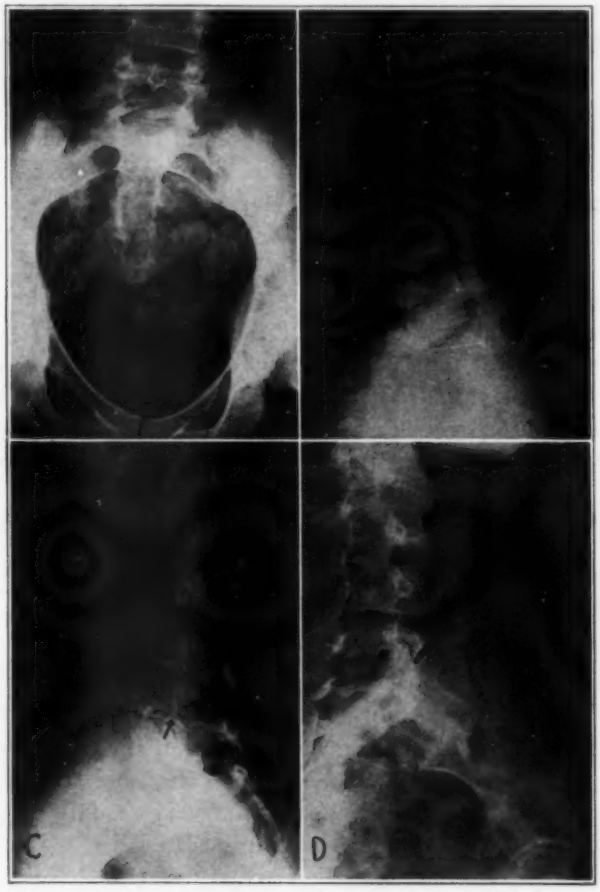

Fig. 5.—*A*, anteroposterior projection. It is normal except for incomplete formation of the spine of the fifth lumbar space. *B*, lateral projection. The body of the fifth vertebra is displaced posteriorly 2 mm. on the sacrum. *C* and *D*, right and left posterior oblique projections. Both interarticular portions of the neural arch of the fifth lumbar space are intact but are unusually short and almost vertical in position. On both sides the lumbosacral joint is anterior to the fourth lumbar intervertebral articulation instead of in the more usual posterior location. The displacement of the body of the fifth lumbar vertebra is therefore due to a bilateral congenitally short pars interarticularis of the neural arch and not to a schistasis of the arch.

In figure 4 the anteroposterior view (*A*) is not remarkable. The lateral projection (*B*) shows a 1 cm. anterior displacement of the fifth lumbar vertebra on the sacrum, with a narrowing of the fifth lumbar disk by approximately one half. In the right posterior oblique projection (*C*), the pars interarticularis of the right lamina is intact through-

out. This is confirmed by stereoscopic views. It is, however, unusually long (congenital elongation) and horizontal in position. The left posterior oblique projection (*D*) shows a 2 mm. defect in the pars interarticularis of the left lamina. This amount of separation is insufficient to account for the 1 cm. displacement of the body. While it is true that the real separation may be somewhat greater than the apparent separation, at least some of the displacement of the vertebral body is due to the unusual length and horizontal position of the pars interarticularis. Thus the anterior displacement of the vertebral body is due not so much to the unilateral bony defect as to the bilateral congenital elongation of the interarticular parts of the lamina.

V. REVERSED SPONDYLOLISTHESIS

In figure 5 the anteroposterior projection (*A*) is not remarkable save for an incomplete formation of the spinous process of the fifth lumbar vertebra. In the lateral projection (*B*), the body of the fifth lumbar vertebra is displaced posteriorly a measurable 2 mm. In the right and left posterior oblique projections (*C*) and (*D*), both interarticular portions of the neural arch of the fifth lumbar vertebra are intact, but both are unusually short and almost vertical in position. In this instance the posterior displacement or reversed spondylolisthesis of the body of the fifth lumbar vertebra is therefore due to a congenitally misshapen neural arch, with abnormal shortening of its interarticular parts.

CONCLUSIONS

Additional and correlated variations of the anomaly in the pars interarticularis or isthmic portion of the neural arch are demonstrated. These include congenital absence of the pars interarticularis, congenital lengthening of the pars interarticularis and congenital shortening of the pars interarticularis as well as the usual defect resulting from failure of fusion of the pars interarticularis with the lamina.

The mechanism for the dislocation of a vertebral body in the presence of a unilateral defect in continuity, involving one side only in the neural arch, is explained on the basis of a demonstrated congenitally elongated pars interarticularis on both sides.

A reversed spondylolisthesis in the presence of an intact neural arch and posterior articulations is demonstrated to be the result of a congenital shortening of the pars interarticularis bilaterally.

For a complete understanding of the exact nature of the anatomic variations, oblique as well as anteroposterior and lateral projections should be included in the roentgenographic study of disability low in the back. In cases of unilateral congenital spondyloschisis, without symptoms before injury to the lower part of the back, oblique views may reveal a recent fracture of the previously intact side. In cases of questionable symptoms, stereoscopic views are valuable.

HIGH PROTEIN THERAPY

Clinical Effectiveness of Oral Administration of a New Protein Preparation As Determined by Nitrogen Balance Studies

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IN A RECENTLY reported study from this laboratory,[1] it was shown that positive nitrogen balances could be consistently obtained in surgical patients with protein deficiency by the parenteral administration of amino acids as the only source of nitrogen. However, this method was not successful as a practical program for restoration of the large losses of nitrogen incurred in the protracted deficiency of protein of such patients. With nitrogen losses estimated to be on the order of 480 Gm., the average positive nitrogen balance of 4 Gm. that was obtained would require one hundred and twenty days of continuous intravenous treatment for complete restitution of protein stores. Such management was obviously impractical if not impossible. The time required could be reduced, it was true, if parenteral injections were supplemented with blood transfusions and with normal oral alimentation.

The need for high intakes of protein or protein digests in patients with severe deficiency of nitrogen has been well recognized.[2] Successful efforts to meet this demand by intubation feeding of protein hydrolysates have been reported.[3] We, too, have frequently made use of

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1. Kozoll, D. D.; Hoffman, W. S., and Meyer, K. A.: Nitrogen Balance Studies on Surgical Patients Receiving Amino Acids, Arch. Surg. **51**:59 (July-Aug.) 1945.

2. Co Tui; Wright, A. M.; Mulholland, J. H.; Carabba, V.; Barcham, I., and Vinci, V. J.: Studies on Surgical Convalescence: I. Sources of Nitrogen Loss Postgastrectomy and Effect of High Amino Acids and High Caloric Intake on Convalescence, Ann. Surg. **120**:99, 1944.

3. Elman, R.: The Oral Use of the Amino Acids of Hydrolyzed Casein (Amigen) in Surgical Patients, Am. J. Digest. Dis. **10**:48, 1943. Lund, C. C., and Levenson, S. M.: Protein in Surgery, J. A. M. A. **128**:95 (May 12) 1945. Co Tui and others.[2]

such methods. However, feeding through an intranasal catheter is burdensome both to the patient and to the hospital staff. It is justified in the immediate postoperative period or other conditions in which normal feeding cannot be maintained, but its discomfort, the risk of esophagitis, the frequently accompanying diarrhea and the psychologic assault produced by the supplanting of normal eating habits with such an unnatural procedure make intubation feeding unsatisfactory. It has become increasingly clear that the ideal high protein therapy in patients able to take food by mouth is the oral administration of a palatable,

TABLE 1.—*Analysis of Essenamine*

Content	Percentage
Total nitrogen	12.5
Moisture	6.5
Fat	3.5
Ash	1.9
Chloride	0.08
Calcium	0.06
Phosphate	0.02
Sulfate	0.2
Iron	0.1
Sodium	0.4
Potassium	0.2

TABLE 2.—*Amino Acid Content of Essenamine as Compared with That of Lactalbumin*

	Essenamine, per Cent	Lactalbumin, per Cent *
Arginine	3.6	3.5 ± 0.5
Histidine	2.2	2.0 ± 0.3
Lysine	8.7	8.0 ± 1.1
Tryptophan	2.5	2.3 ± 0.3
Phenylalanine	5.4	5.6
Methionine	3.5	2.8 ± 0.2
Threonine	6.8	5.3
Leucine	12.0 }	15
Isoleucine	7.5 }	
Valine	6.8	4
Cystine	2.7	3.0 ± 0.2
Tyrosine	4.6	5.3 ± 0.1

* Block, R. J., and Bolling, D.: The Amino Acid Composition of Proteins and Foods: Analytical Methods and Results, Springfield, Ill., Charles C Thomas, Publisher, 1945, p. 303.

easily digested protein or protein derivative capable of being incorporated in large quantities in the common foods and of producing large positive nitrogen balances.

Recently a new processed protein, called Essenamine, has been made available to us for study.[4] This product is a yellowish white, nonhygroscopic powder obtained by partial alkaline degradation of lactalbumin. It contains, by our analysis, 12.5 per cent nitrogen. Its content of amino acids, as furnished to us by the manufacturers and listed in table 1, indicates that it is a complete protein not significantly different in

4. Furnished by Frederick Stearns & Company, Detroit.

amino acid content from the lactalbumin from which it was prepared. It is only slightly soluble in water and is incorporated as a suspension in the solid or liquid food items of the diet. It has no odor and no pronounced taste. Its presence can easily be masked by other foods, except so far as it makes these foods "heavier" and dilutes their taste. The product appears to be stable indefinitely even when kept in bulk without any special precautions.

It was the purpose of this investigation to make a clinical evaluation of Essenamine, first, by determining the minimal amount of Essenamine required for nitrogen equilibrium and, second, by treating patients with large quantities of Essenamine in addition to normal foods and ascertaining, through nitrogen balance studies and through determinations of plasma volume and serum protein levels, what degree of nitrogen retention and protein restitution was possible. At the same time an effort was to be made to determine whether the use of Essenamine was a practical dietetic procedure.

METHODS

Fourteen surgical patients with protein deficiency who were able to take food by mouth were studied in a metabolic unit. This unit was staffed by special nurses over the twenty-four hour period and by special dietitians. Careful balance studies were carried out in which the foods were accurately weighed or measured and steps taken to see that the subjects cooperated by eating all the food offered them. All specimens of urine for the twenty-four hour periods were collected in bottles containing toluene. Stools were kept for analysis in large covered beakers containing toluene. When other excretions occurred, such as from fistulas, these were collected. The total excretions were analyzed for the twenty-four hour periods by micro-Kjeldahl methods as modified by Hoffman and Osgood.[5] The stools were first homogenized in water, with the aid of concentrated sulfuric acid, as suggested by Peters and Van Slyke.[6] The nitrogen content of the sample diets was similarly determined. Estimations of plasma volume were made by the Evans blue method, in which a single ten minute sample was used, as recommended by Gregerson.[7] The determination was carried out in the morning, breakfast having been withheld and no food given since the previous evening meal. Since none of the patients had any recognizable circulatory impairment, ten minutes was believed to be adequate for complete mixing of the injected Evans blue. Determinations of hematocrit levels were made on heparinized blood in Wintrobe tubes. Analyses of serum albumin were made by the method of Campbell and Hanna.[8]

Eleven of the 14 patients were first placed on the minimal Essenamine diet. Later, when the minimal requirements for nitrogen balance had been determined,

5. Hoffman, W. S., and Osgood, B.: The Photoelectric Microdetermination of Nitrogenous Constituents of Blood and Urine by Direct Nesslerization, J. Lab. & Clin. Med. **25**:856, 1940.

6. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams and Wilkins Company, 1932, vol. 2, p. 78.

7. Gregerson, M. I.: A Practical Method for the Determination of Blood Volume with the Dye T-1824, J. Lab. & Clin. Med. **29**:1266, 1944.

8. Campbell, W. R., and Hanna, M. I.: The Albumins, Globulins, and Fibrinogen of Serum and Plasma, J. Biol. Chem. **119**:15, 1937.

9 of the same patients were placed on high Essenamine diets. In experiments with 3 additional patients, only the high Essenamine diet was used. In the latter group, the preparation of Essenamine used contained much more sodium chloride and less nitrogen than that used for all other experiments (see table 4), though it was prepared from lactalbumin in essentially the same manner.

The initial diet for the determination of the minimal protein requirement consisted of Essenamine mixed with foods which contained little or no nitrogen. It was found impossible to get the cooperation of the patients if the foods were such as to be completely devoid of nitrogen. Therefore a compromise had to be made by the use as vehicles for the Essenamine of the fruits and vegetables which contained 1 per cent or less of protein, as determined from accepted tables [9] and confirmed by nitrogen analyses. Though admittedly such a procedure could not have the same significance as that in which all other sources of nitrogen were rigidly excluded—as could be accomplished with laboratory animals or with normal human volunteers—it was unlikely that any great error was introduced, for the daily quantity of extraneous nitrogen represented only 6 to 7 per cent of the total nitrogen of the diet and the proteins involved were known to be of inferior biologic value. It was extremely unlikely that the small quantities of these proteins from leafy vegetables or from fruits could furnish significant amounts of any essential amino acids that might be missing from the Essenamine diet.

The food for the minimal diets was prepared in three forms: (1) a drink containing Essenamine, oil and sugar in an agar solution (when little water was used, the cooled preparation became a custard); (2) a sauce containing Essenamine, for vegetables or for use as a thick soup, and (3) a fruit "crisp" containing Essenamine. The method of preparation of these foods is given in the appendix. The diet furnished some 2,000 calories. Preliminary trials were made to determine the approximate quantity of Essenamine necessary for positive nitrogen balance, since it was impractical to place the patients on a graduated program, with increasing quantities of protein, such as was used by Allison [10] with dogs. The amount finally chosen was 60 Gm. of Essenamine, and this quantity was given regardless of the weight of the patients. An occasional failure of a subject to eat one of the food items sometimes modified this intake.

For the experiments with large amounts of Essenamine, the plan was to determine the extent of nitrogen retention and clinical improvement that occurred when Essenamine was given as a supplement to ordinary foods. The latter were kept as constant as possible and except for the milk used were relatively low in proteins. The nitrogen content of these foods was calculated from accepted tables [9] but was checked by sample analyses of the whole daily diet. The errors involved were too small to influence considerably the amount of positive nitrogen balance, particularly since the nitrogen of the milk of the diet, which constituted the chief portion of the extraneous nitrogen, was determined by direct analysis. Essenamine was given in most of the experiments chiefly in the form of a concentrated milk shake, which proved palatable. This drink was made to contain 150 Gm. of Essenamine per 1,500 cc., which was offered daily to the subjects. They were requested to drink a glass at a time during the day in addition to their small regular meals. Essenamine was also furnished in the form of cookies, biscuits or fruit pudding, all of

9. Chatfield, C., and Adams, G.: The Proximate Composition of American Food Materials, Circular no. 549, United States Department of Agriculture, 1940.

10. Allison, J. B., and Anderson, J. A.: The Relation Between Absorbed Nitrogen, Nitrogen Balance and Biological Value of Proteins in Adult Dogs, J. Nutrition **29**:413, 1945.

TABLE 3.—*Minimal Essenamine Requirement for Nitrogen Balance*

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Case	Diagnosis	Weight, Kg.	Days on Diet	Average Daily Essenamine Intake: Gm. Protein	Average Daily Essenamine Intake: Gm. Nitrogen	Average Daily Additional Nitrogen Intake	Total Nitrogen Intake, Gm.	Total Nitrogen Excretion, Gm.	Nitrogen Balance: Total	Nitrogen Balance: Gm. per Kg. per Day	Daily Intake per Kg. Body Weight: Gm. Protein	Daily Intake per Kg. Body Weight: Gm. Nitrogen
1.	Gastritis	62.7	7	72.8	9.10	0.57	67.7	62.6	+ 5.1	0.0126	1.16	0.15
2.	Carcinoma of the sigmoid	70	8	75.0	9.38	0.57	79.1	61.2	+17.9	0.0320	1.07	0.14
3.	Carcinoma of the stomach	49	9	60	7.50	0.48	71.8	56.4	+15.4	0.0350	1.28	0.16
4.	Pelvic inflammatory disease	49	9	60	7.50	0.48	71.8	66.0	+ 5.8	0.0132	1.28	0.16
5.	Carcinoma of the rectum	40	9	48.7	5.86	0.40	56.3	53.4	+ 2.9	0.0081	1.28	0.15
6.	Neurofibroma of the stomach	47.5	8	58.1	7.17	0.46	61.9	58.7	+ 3.2	0.0084	1.28	0.15
7.	Pancreatic fistula	41.4	6	56.2	7.03	0.45	44.9	62.16	—17.2	—0.0692	1.42	0.17
8.	Carcinoma of the rectum	55	8	60	7.50	0.48	63.8	38.51	+25.3	0.0575	1.14	0.14
9.	Varicose ulcer	54	10	60	7.50	0.48	79.8	74.8	+ 5.0	0.0093	1.16	0.14
10.	Varicose ulcer	58.5	10	60	7.50	0.48	79.8	50.2	+29.6	0.0506	1.07	0.13
11.	Varicose ulcer	90	9	60	7.50	0.48	71.8	80.4	— 8.6	—0.0106	0.70	0.08
		90	4	90	11.25	0.72	47.9	39.6	+ 8.3	0.0231	1.05	0.13

TABLE 4.—*Nitrogen Balance Studies with Large Amounts of Essenamine*

Case	Diagnosis	Weight, Kg.	Days on Diet	Average Daily Essenamine Intake: Gm. Protein	Average Daily Essenamine Intake: Gm. Nitrogen	Average Daily Additional Nitrogen Intake	Total Nitrogen Intake, Gm.	Total Nitrogen Excretion, Gm.	Nitrogen Balance: Total	Nitrogen Balance: Per Day	Daily Intake per Kg. Body Weight: Gm. Protein	Daily Intake per Kg. Body Weight: Gm. Nitrogen
1.	Gastritis	62.7	7	180	22.5	7.5	209.8	155.2	+ 54.6	7.8	4.30	0.48
3.	Carcinoma of the sigmoid	49	26	150	18.75	8.0	698.0	449.8	+248.2	9.5	4.08	0.54
4.	Pelvic inflammatory disease	49	18	155	19.45	7.4	484.0	375	+109	6.6	4.15	0.54
5.	Carcinoma of the rectum	40	15	118	14.7	7.25	330	116.0	+214.0	14.3	4.07	0.55
6.	Neurofibroma of the stomach	47.5	20	136	17.0	9.9	538	341.3	+196.7	9.8	4.12	0.56
7.	Pancreatic fistula	41.4	20	144	18.0	9.0	542.2	317.0	+225.2	11.3	4.80	0.65
9.	Varicose ulcer	54	10	170	21.25	15.7	369.0	195.7	+173.3	17.3	4.9	0.68
10.	Varicose ulcer	58.5	10	170	21.25	15.5	367.5	159.8	+207.7	20.8	4.5	0.62
11.	Varicose ulcer	90	9	168	20.8	10.9	286.5	216	+ 70.5	7.8	2.6	0.35
*12.	Empyema	58	17	219	20.8	3.1	415.4	229	+186.4	11.0	4.09	0.41
*13.	Burn	53	18	223	21.2	3.0	436.0	175.7	+249.7	13.9	4.55	0.45
*14.	Empyema	62.5	18	283	28.3	3.7	602.7	289.7	+313.0	17.4	4.89	0.51
								Average			4.25	0.52

* The preparation of Essenamine given in cases listed here contained 10 Gm. of sodium chloride and 9.5 Gm. of nitrogen per hundred grams; all other preparations contained 1.5 Gm. of sodium chloride and 12.5 Gm. of nitrogen per hundred grams.

which were acceptable. The material also could be incorporated in cereals and vegetables. The latter were vehicles for the Essenamine with the high salt content for 3 subjects (cases 12, 13 and 14 in table 4). The exact composition of the prepared foods is given in the appendix. The caloric intake varied between 2,500 and 3,000 calories. Maintenance doses of vitamins B and C were provided for, in experiments both with the high and with the low Essenamine content, as adjuvant medication.

RESULTS

Minimal Essenamine Requirements.—The 11 subjects placed on the minimal diet ingested from 48.7 to 90 Gm. of Essenamine daily, or from 5.86 to 11.25 Gm. of Essenamine nitrogen daily (see table 3). The additional nitrogen intake was usually of the order of 0.5 Gm. Positive nitrogen balance was achieved in ten of the experiments. The nitrogen per kilogram per day required for this achievement ranged from 0.13 to 0.16 Gm. per day. Patient 11, who weighed 90 Kg., was unable to achieve positive nitrogen balance on 0.08 Gm. per kilogram per day but did so on 0.13 Gm.

Patient 7 failed to show a positive nitrogen balance during the six days of study, in spite of an intake of 0.17 Gm. per kilogram per day. This patient had been extremely ill just previous to the experimental study. She had a pancreatic fistula and had suffered from severe dehydration and extrarenal azotemia. Parenterally injected fluids had lowered the blood nonprotein nitrogen level from 131 to 50 mg. per hundred cubic centimeters and had raised the plasma volume from 1,450 to 2,030 cc. It was at this stage that the nitrogen balance study was begun. It was not improbable that some of the excreted nitrogen represented previously retained nonprotein nitrogen. At any rate, since the results from this patient are completely at variance with those from the others, they should probably be discarded in the evaluation of the minimal requirements for nitrogen balance.

The average daily nitrogen intake in the ten experiments in which positive nitrogen balance was achieved was 0.145 Gm. per kilogram per day. In these ten experiments the average positive nitrogen balance was 11.85 Gm. per person, or 0.0249 Gm. per kilogram per day. To determine the average daily Essenamine nitrogen requirement for exact nitrogen balance, it is necessary to know the slope of the curve relating nitrogen intake to nitrogen balance, which Allison[10] has shown to be a straight line near the region of zero nitrogen balance. Unfortunately, the experiments were not designed to show such a slope. Balances at various levels of nitrogen intake were not determined except in case 11. In this case there were two levels of intake. If one plots, as in chart 1, the two points of the experiment and draws a line between them, then the remaining nine points similarly plotted will be found to fall reasonably well on either side of this line. The average for the ten experiments with positive nitrogen balance, represented by *X* in chart 1, falls near

the sloping line. If it is assumed that the line drawn for case 11 has the average slope for all the 10 patients with positive nitrogen balance, then another line drawn through *X* parallel to this line will pass through the base line of zero nitrogen balance at the point defining the average intake required for exact nitrogen balance. This point is slightly less than 0.11 Gm. per kilogram per day. Even if these assumptions are unwarranted, the calculation based on them gives some notion of the average intake required and it is reasonably certain that it is

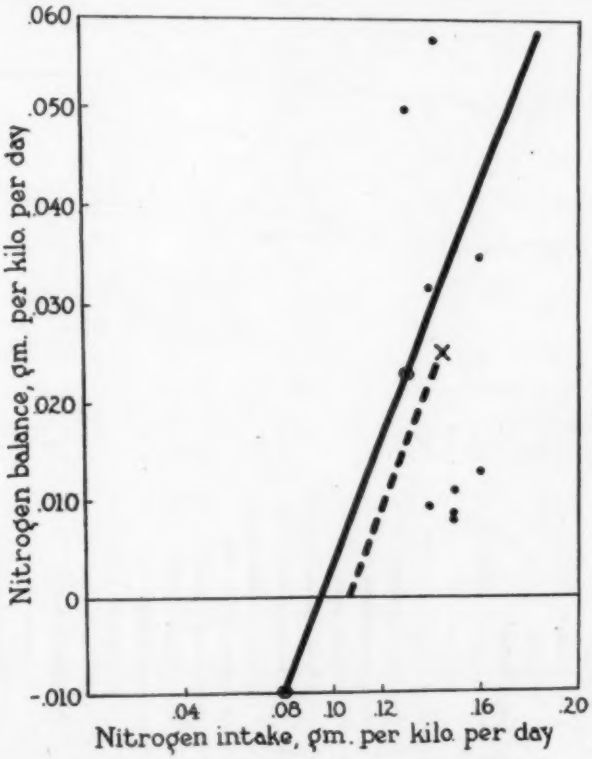

Chart 1.—The relation of nitrogen balance to nitrogen intake at low levels. The solid black line represents two levels of intake in 1 patient (one with negative balance and one with positive). The points representing the results in 9 other subjects with positive nitrogen balance fall on both sides of this line. The average for all ten experiments is represented by *X*. The line through *X* parallel to the solid line intersects the zero balance line at the level of average intake for exact nitrogen balance, a little less than 0.11 Gm. per kilogram per day.

appreciably less than the 0.145 Gm. per kilogram required for the moderately positive nitrogen balance of these experiments.

High Essenamine Diets.—The experiments were originally designed to determine the upper limits of protein intake attainable with the preparation used, but it was soon recognized that for a number of patients this would involve the frequent rejection of part of the food

offered. Since the measurement of such unused food makes for considerable error in the determination of nitrogen balance, it was decided to stay within the limits imposed by the patients, who for the most part had no conception of the nature of the experiment. It was possible even in these circumstances to accomplish the ingestion in 12 out of 14 cases of more than 0.45 Gm. nitrogen per kilogram per day, or about four times the estimated minimal requirements (see table 4).

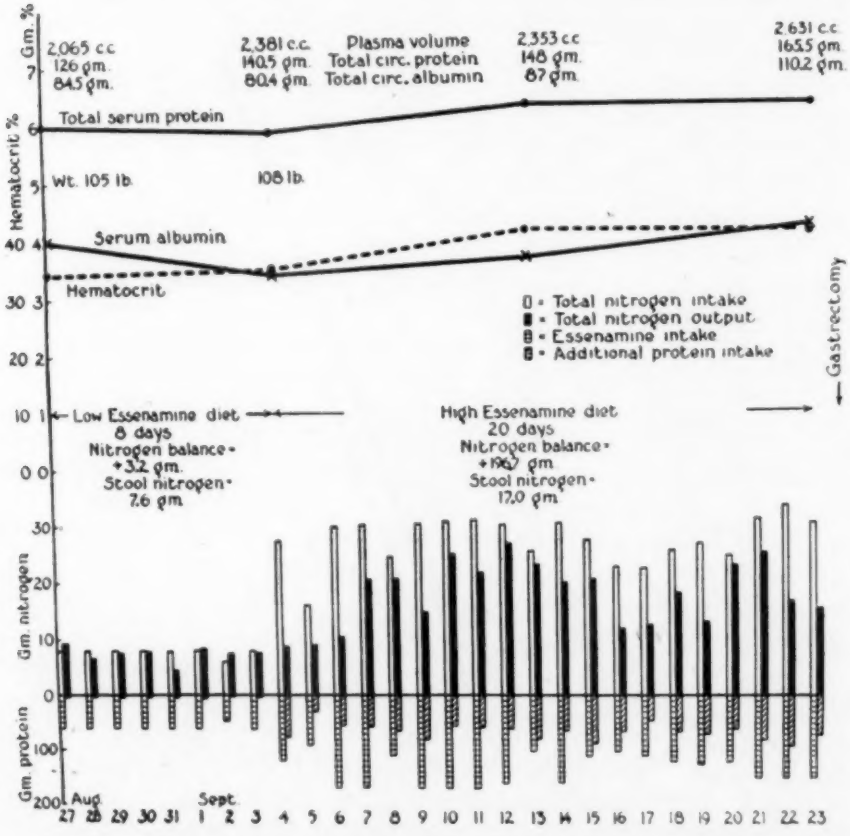

Chart 2.—Daily nitrogen balance record, with Essenamine as the principal source of protein given orally, of a 56 year old patient with neurofibroma of the stomach prepared for a transthoracic gastrectomy. On the low Essenamine diet the patient retained 5.4 per cent of the ingested nitrogen; on the high Essenamine diet this patient retained 36.5 per cent. There was a progressive increase in the plasma volume, total circulating protein and albumin in addition to a 7 pound (3.2 Kg.) gain in weight and general definite clinical improvement (case 6).

In all twelve experiments there was large retention of nitrogen, ranging from 6 to 20 Gm. daily, with an average of 12 Gm. per day. In all cases, too, there was an increased sense of well-being, gain in weight and strength and a steady improvement in appetite. There was no

elevation of nonprotein nitrogen above normal limits. The daily courses in three of the experiments are shown in charts 2, 3 and 4.

Comparison of the distribution of the absorbed nitrogen in the minimal and in the high protein diet (as seen in table 5) shows that there

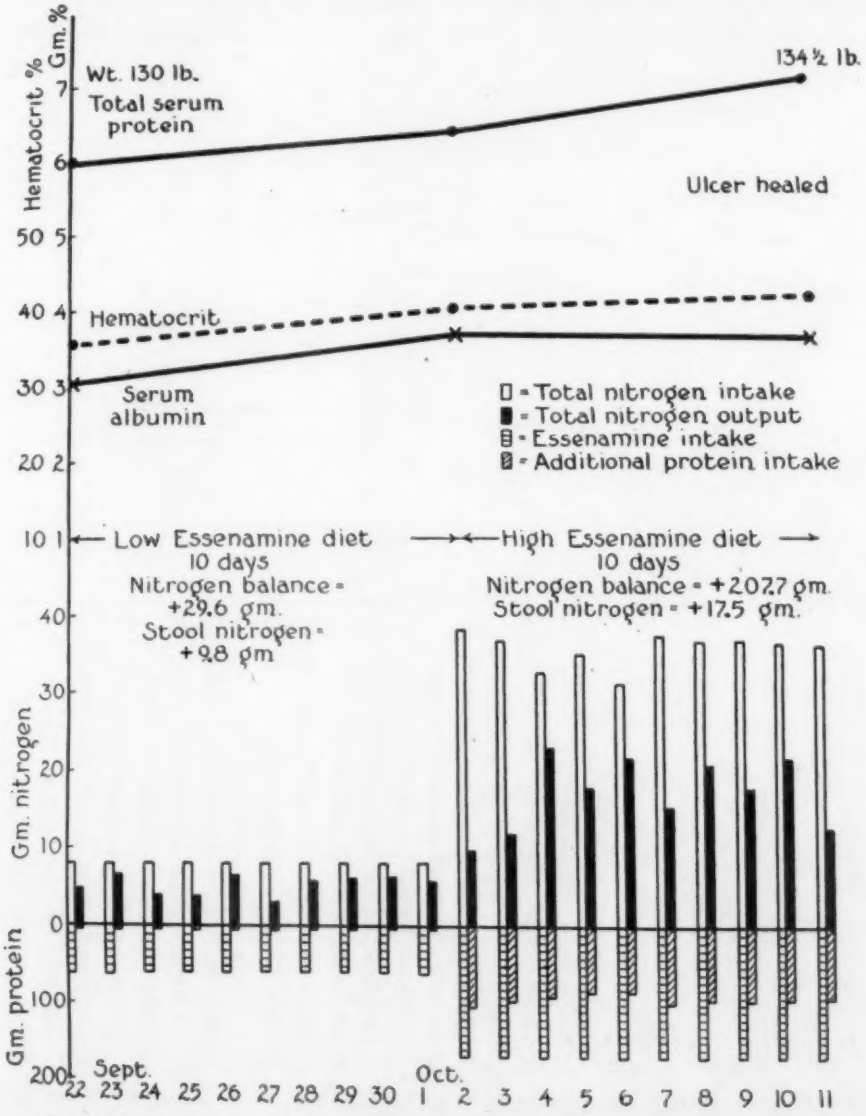

Chart 3.—Daily nitrogen balance studies in a 41 year old patient with alcoholic malnutrition and delayed healing of varicose ulcer. A substantial positive nitrogen balance occurred with both the low and the high Essenamine diet. The total serum protein content rose from 5.96 to 7.01 Gm. per hundred cubic centimeters, while the serum albumin level rose from 3.08 to 3.58 Gm. per hundred cubic centimeters. Gain in weight and improvement in wound healing and clinical appearance corresponded with these findings (case 10).

was little increase in fecal nitrogen on the high protein diet. The average daily fecal nitrogen for the low protein diet was 1.03 Gm., and for the high protein diet it was 1.47 Gm. This finding indicates the high degree of digestibility (and absorbability) of the proteins fed. The coefficient of digestibility for the total protein fed on the high Essenamine diet was 0.95, that is, 5 per cent of the ingested nitrogen

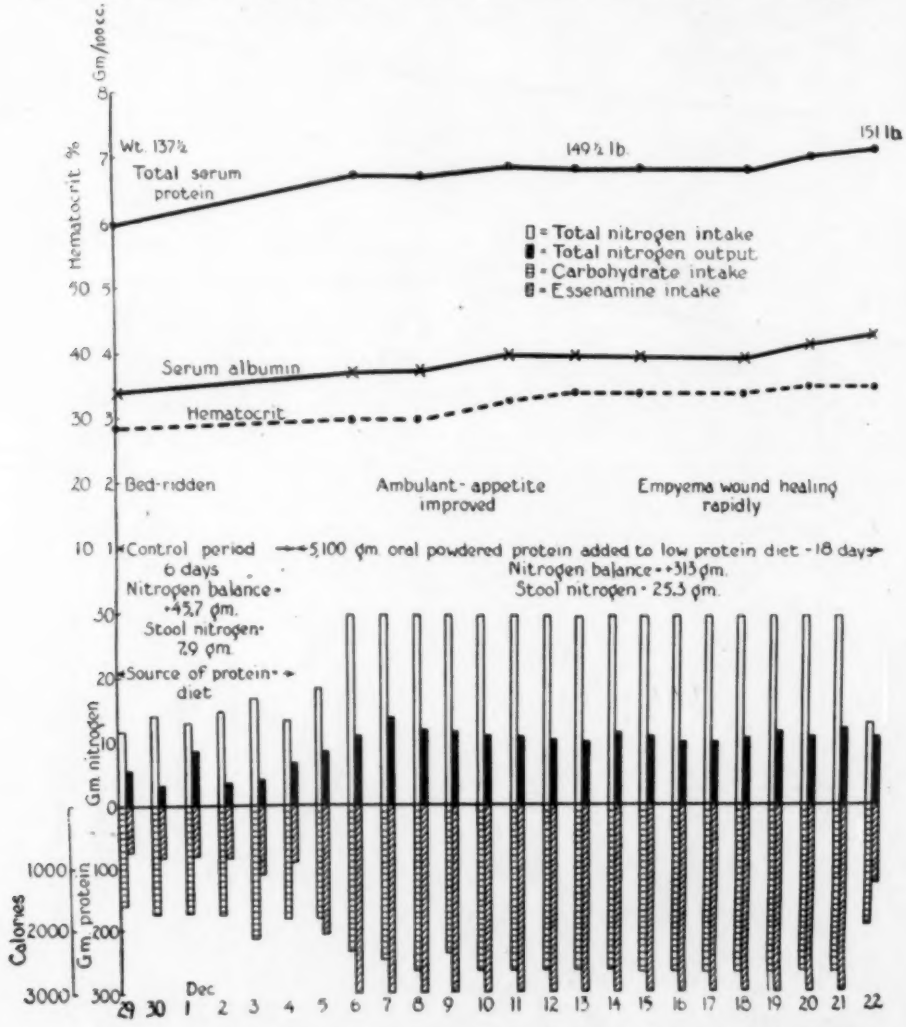

Chart 4. —Daily nitrogen balance studies, with Essenamine as the principal source of protein given orally, on a 28 year old patient with empyema of the chest who ingested 300 Gm. of protein daily for seventeen days. This particular form of Essenamine contained 9.5 Gm. of nitrogen and 10 Gm. of sodium chloride per hundred grams. The patient retained 51.8 per cent of the ingested nitrogen. This was associated with a 13½ pound (6.1 Kg.) gain in weight and an increased urinary output. The total serum protein content rose from 5.97 Gm. per hundred cubic centimeters to 7.23 Gm. per hundred cubic centimeters and the serum albumin level from 3.4 to 4.34 Gm. per hundred cubic centimeters (case 14).

was found in the feces. Since the coefficient of digestibility of casein is rated at 0.96 and that of vegetable and cereal proteins somewhat lower, then the digestibility of Essenamine is on the same order as that of casein. Such a finding is especially significant in that Essenamine has a limited solubility. A good portion of it might have been expected to pass through the bowel unabsorbed.

On the high protein diet the small absolute increase in fecal nitrogen lowered the percentage of total nitrogen in the feces from 11.8 to 5.0 per cent. Similarly, the urinary nitrogen on the high protein diet,

TABLE 5.—*Fate of Nitrogen Ingested in Essenamine Diet*

Case No.	Essenamine Diet	Nitrogen Ingested, Gm.	Excreted in Urine, per Cent	Stool Excretion		Retained, per Cent
				Gm. Nitrogen per Day	Per Cent	
1.....	Low	67.7	76.2	1.71	16.2	7.6
	High	209.8	65.3	2.54	8.5	26.2
2.....	Low	79.1	63.2	1.39	14.1	22.7
3.....	Low	71.8	66.7	0.94	11.8	21.5
	High	698.0	57.5	1.83	6.8	35.8
4.....	Low	71.8	84.7	0.56	7.1	8.2
	High	484.0	66.6	2.55	9.5	23.9
5.....	Low	56.3	87.0	0.49	7.8	5.2
	High	380.0	31.5	1.03	4.7	63.8
6.....	Low	61.9	82.4	0.94	12.2	5.4
	High	538.0	60.4	0.83	3.1	36.5
7.....	Low	44.9	135.0*	0.21	2.87	—37.8*
	High	542.2	53.2	1.33	4.9	41.9
8.....	Low	63.8	34.0	2.09	26.3	39.7
9.....	Low	79.8	85.8	0.63	7.9	6.3
	High	369.0	48.6	1.62	4.4	47.0
10.....	Low	79.8	50.6	0.97	12.2	37.2
	High	367.5	38.7	1.73	4.7	56.6
11.....	Low	71.8	96.7	1.21	15.2	—11.2*
	Low	47.2	74.0	1.17	9.9	16.1
	High	286.5	71.8	1.21	3.8	24.4
12.....	High	415.4	52.1	0.93	3.8	44.1
13.....	High	436.0	37.6	0.61	2.5	59.9
14.....	High	602.7	44.1	1.37	4.1	51.8
Average.....	Low	.....	78.05	1.08	11.8	11.7
	High	.....	52.2	1.47	5.0	42.6

* Negative nitrogen balance.

though increased absolutely, diminished relatively, the percentage of total nitrogen intake dropping from 78 per cent to 52.2 per cent. Thus the percentile retention of nitrogen increased from 11 per cent on the low protein diet to 43 per cent on the high protein diet. In other words, nearly half of the ingested nitrogen was retained by these subjects. These results are in sharp contrast to the 23 per cent retention of the intravenously injected nitrogen when maximal quantities were administered.[1]

Systemic Effects of the High Protein Diet.—As has been stated, the large retention of nitrogen in protein-deficient subjects as shown even in those relatively brief experiments was reflected in an increased

sense of well-being, improvement in appetite and usually a moderate gain in weight. Some of these improvements occurred even when the subjects were on the maintenance diet. Here they may have meant chiefly a restoration of water and mineral balance. This was supported by the fact that the hematocrit level was usually lower at the end of the maintenance period than at the start of the experiment. On the high protein diet, the gain in weight usually continued and was in many cases a genuine gain in flesh, for in this period the hematocrit values usually increased.

Table 6 shows the effect of the dietary regimen on the weight, hematocrit level, serum protein content and plasma volume for all the experiments. (Determinations of plasma volume were made in only eight experiments.) The early fall in hematocrit values was paralleled by a drop in serum protein concentration, the two being consequences of hemodilution. Estimations of plasma volume confirmed this trend, but the increase in plasma volume was not necessarily on the same order as the rise in hematocrit content. This phenomenon has been well demonstrated by Abbott and Mellors.[11] On the high protein diet, the serum protein concentration rose in 9 cases and decreased in 3. Of the latter, only 1 case represented a decrease in albumin concentration. In case 4 a drop in serum protein concentration actually represented a fall in an abnormally high concentration of serum globulin to normal during the period of study. This was a case of chronic pelvic inflammatory disease. In the 8 cases in which estimations of plasma volume were made, the improvement in serum protein production, especially that of serum albumin, could be better recognized by a study of the total circulating proteins. In all eight experiments there was a rise in total circulating albumin. In 6 of the 8 cases, the rise was considerable.

COMMENT

Though the need for a high protein diet to combat the effects of low concentrations of serum protein and their accompanying deficiency of tissue protein have been recognized since 1917, when Epstein[12] recommended such diets for the treatment of nephrosis, the difficulties of achieving satisfactory high protein alimentation have never been overcome. A sick patient can seldom be forced to eat a natural diet containing more than 100 Gm. of protein for any extended period, whether the chief source of protein is meat, milk or cheese. The bulk is too great, and the sense of fulness and satiation is overwhelming. It is necessary to add protein or its equivalent in a concentrated form.

11. Abbott, W. E., and Mellors, R. C.: Total Circulating Plasma Proteins in Surgical Patients with Dehydration and Malnutrition, Arch. Surg. **46**:277 (Feb.) 1943.

12. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation, Am. J. M. Sc. **154**:638, 1917.

TABLE 6.—*Effect of Essenamine Diets on Circulating Proteins*

TABLE 6.—*Effect of Essenamine Diets on Circulating Proteins*

Case No.	Essenamine Diet	Initial Weight, Kg.	Weight Gain, Kg.	Nitrogen Balance, Gm.	Hematocrit Level, per Cent	Total Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Plasma Volume, Cc.	Total Circulating Protein, Gm.	Total Circulating Albumin, Gm.
1	Control	62.7	...	.....	46	6.35	3.76	2,500	158.5	94.0
	Low	....	0.8	+ 8.5	49.5	6.82	4.07	2,083	142.6	84.5
	High	....	1.3	+ 54.6	49	6.98	4.41	3,030	201.8	133.1
2	Control	70	...	.....	45	5.31	3.50	2,857	151.7	99.8
	Low	....	0	+ 17.5	42	5.60	3.51	3,175	177.5	111.5
3	Control	49	...	.....	45	6.28	4.35	1,808	113.4	78.0
	Low	....	0	+ 15.4	40.5	5.86	3.87	1,754	102.4	68.8
	High	....	1.5	+ 47.2	46.5	7.01	4.84	2,128	149.8	103.2
4	Control	49	...	.....	40	8.12	4.09	2,817	228.4	115.3
	Low	....	0	+ 5.8	36	7.50	4.16	2,566	195.6	107.6
	High	....	1.2	+109.0	36.5	7.13	4.33	2,703	193.2	117.0
5	Control	40	...	.....	29.5	6.33	3.83	2,456	155.4	93.8
	Low	....	0	+ 2.9	32	6.54	4.60	2,300	150.5	105.7
	High	....	5	+214.0	43	7.10	4.30	2,632	187.0	113.2
6	Control	47.5	...	.....	34	6.08	4.05	2,065	126.0	84.5
	Low	....	1.2	+ 3.2	35	5.89	3.37	2,381	140.5	80.4
	High	....	1.8	+196.7	41	6.29	4.19	2,631	165.5	110.2
7	Control	41.4	...	.....	52	6.65	3.84	2,083	139.6	80.0
	Low	....	6.3	— 17.2	46.5	6.71	4.05	2,298	155.0	92.9
	High	....	2.7	+225.0	40	6.31	4.51	2,865	180.5	131.2
8	Control	55	...	.....	48	5.65	3.25	2,000	113.2	65.0
	Low	....	0.9	+ 25.3	39	6.28	4.18	2,353	148.0	99.2
9	Control	54	...	.....	45	6.43	2.93			
	Low	....	2.0	+ 5.0	47	6.39	2.99			
	High	....	0.6	+173.3	43	6.73	3.04			
10	Control	58.5	...	.....	35.5	5.96	3.08			
	Low	....	1.3	+ 29.6	40	6.36	3.65			
	High	....	0.6	+207.7	41.5	7.01	3.58			
11	Control	90	...	.....	51	6.52	4.18			
	Low	....	0	+ 8.6	49	6.12	4.37			
	High	....	0.9	+ 70.5	48	7.11	5.23			
12	Control	58	...	.....	37	7.13	2.60			
	High	....	1.5	+186.4	31.5	6.98	3.23			
13	Control	83	...	.....	31	5.83	3.88			
	High	....	1.2	+249.7	31.5	6.12	3.72			
14	Control	62.5	...	.....	28.5	5.97	3.41			
	High	....	6.3	+313.0	35.5	7.23	4.34			

The use of such products as dried skim milk, soya protein, peanut flour, dried brewers' yeast and wheat or corn germ has recently been discussed by Turner.[13] Even when these products are incorporated as dry products in the daily food items, it has been difficult to get above 150 Gm. of protein daily, because all these items usually contain less than 50 per cent protein and because they have a pronounced taste, which though not unpleasant becomes monotonous and tiresome.

The use of protein digests for oral alimentation has to date proved disappointing. Hydrolysates of protein, whether prepared by enzyme or by acid, have a bad taste that eventually proves nauseating. A patient may be persuaded to take some in a disguised form for a few days, but long before a demonstrable nutritional effect can be produced he will usually have rebelled at a continuance of this regimen. In such cases feeding by intranasal tube may be resorted to, and, as has been stated, this can at times be successful. But most often such feeding defeats its own purpose by destroying whatever vestige is left of the appetite for normal foods.

Our success with the employment of Essenamine as the principal ingredient of a high protein diet was probably due to four factors: (1) its high concentration of proteins (with 12.5 per cent nitrogen, its protein content can be regarded as 81.3 per cent, if Essenamine has the same nitrogen factor of 6.5 that lactalbumin has[14]); (2) its high content of essential amino acids, that is, its high biologic value as indicated from the fact that about 0.11 Gm. of nitrogen per kilogram per day were required in our experiment for nitrogen balance; (3) its lack of any pronounced taste, so that it can be incorporated in large quantities in other foods that have a pleasant taste, and (4) its limited solubility. The last of these qualities could not have been anticipated as being a virtue. It had been feared that the relative insolubility would limit the digestibility and absorbability of the protein. But this did not prove to be the case, as shown by the low content of fecal nitrogen. On the other hand, the limited solubility apparently minimized the concentration of amino acids in the small intestine at any one time, so that the sense of fulness was postponed and the tendency to diarrhea, which has been frequently present in intubation feedings of protein hydrolysates, did not occur.

For the purpose of simplicity in the management of the nitrogen balance experiments, the number of foods in which Essenamine was incorporated was small, but for other patients, for whom no balance

13. Turner, D. F.: Selection of Protein Containing Foods to Meet Protein Requirements, J. A. M. A. **128**:590 (June 23) 1945.

14. Jones, D. B.: Factors for Converting Percentages of Nitrogen in Foods and Feeds into Percentages of Protein, Circular no. 183, United States Department of Agriculture, 1931.

studies were carried out, Essenamine was incorporated in tasty preparations of many foods. These include bread, cookies, candies, sandwich spreads, meat sauces, vegetable sauces, cereals, fruit crisps, puddings, custards and milk drinks. Such a variety of dishes is of particular value in the home management of protein deficiency, where special care and individual attention may be devoted to the needs and tastes of the patient. Even in the hospital, many of these dishes can be prepared without any great extension of the activities of the dietetic department. In the simplest form, the protein can be suspended in milk or orange juice immediately before being administered.

In the experiments with the minimal Essenamine requirements, the limitations imposed by the experiment made for a monotonous diet, so that it could not be protracted for any long period. But in the high protein diets, the menus offered were regarded as satisfactory by the patients and could have been continued for a longer period than the actual duration of the experiments. It was the rigor of the nitrogen balance regimen that determined the length of the experiment.

There was no recognizable correlation of the quantity of nitrogen retained per day with the initial concentrations of serum protein or with the rise of serum protein concentration to normal limits, though such correlations might have been expected. Possibly this was due to the fact that none of the patients had extremely low levels of serum protein. Also there was no indication of a tapering of the amount of positive nitrogen balance as the experiments progressed (charts 2, 3 and 4), even though in a number of cases the serum protein concentration had apparently returned to normal values. This finding might mean either that the serum protein concentration could return to normal before the body stores of protein had been fully repleted or that nitrogen compounds might be temporarily stored beyond the body needs. The former explanation was more likely to be the correct one, especially since the clinical appearance of the patients and their relatively small gain in weight implied that they were far from restored to normal condition during the period of the experiments.

The actual time required for complete restitution of body protein stores with our high protein regimen could not be determined from the experiments. However, it can be pointed out that in the several cases in which these experiments preceded surgical treatment the patients underwent the operation well and had good postoperative courses. Also the patients who were placed on this diet postoperatively convalesced rapidly and without complications.

SUMMARY AND CONCLUSIONS

1. Fourteen surgical patients were studied in nitrogen balance experiments to determine the clinical effectiveness of Essenamine, a

new processed protein derivative of lactalbumin, as a high protein therapeutic agent.

2. In ten of eleven experiments to determine the minimal nitrogen requirement of Essenamine for nitrogen balance, positive nitrogen balance was achieved with an intake of 0.145 Gm. of nitrogen per kilogram per day. For exact nitrogen balance, it was estimated that 0.11 Gm. per kilogram per day would be required.

3. On the minimal intake of Essenamine, 78 per cent of the ingested nitrogen was excreted in the urine, 11 per cent was excreted in the feces and 11 per cent was retained in the body.

4. In twelve balance experiments in which Essenamine was used as the main ingredient of a high protein diet for periods ranging from seven to twenty-six days, 0.52 Gm. of nitrogen per kilogram per day was given orally. This diet produced positive nitrogen balances ranging from 6 to 20 Gm. of nitrogen per day, with an average of 12 Gm.

5. On the high Essenamine intake, 52.2 per cent of the ingested nitrogen was excreted in the urine, 5 per cent was excreted in the feces and 42.8 per cent was retained, indicating the high digestibility and the high biologic value of proteins ingested.

6. Both the maintenance and the high protein diet usually produced increases in body weight plasma volume, serum protein and serum albumin concentrations and total circulating albumin, but there was no good correlation between these responses and the amount of positive nitrogen balance.

7. Essenamine can easily be incorporated in a large variety of liquid and solid foods to make palatable preparations. Its use as a means of producing a high protein diet is a practical procedure, which has none of the limitations of parenteral or intubation therapy.

APPENDIX

I. Diet for minimal intake of Essenamine for nitrogen balance

A. Menu

1. Breakfast

Orange
Essenamine drink (5 Gm. of Essenamine)
Essenamine custard (5 Gm. of Essenamine)
Hot tea

2. Lunch

Vegetable puree (7.5 Gm. of Essenamine)
Fruit crisp (7.5 Gm. of Essenamine)
Essenamine drink (10 Gm. of Essenamine)

3. Supper

Vegetable puree (7.5 Gm. of Essenamine)
Fruit crisp (7.5 Gm. of Essenamine)
Essenamine drink (10 Gm. of Essenamine)

Total Essenamine 60 Gm.
Total calories about 2,100.
Carbohydrate 260 Gm. (approximately), protein 60 Gm. and fat 90 Gm.

B. Recipes

1. Custard and drink (for one day)

25 Gm. tapioca flour	30 Gm. Essenamine
25 Gm. sugar	80 Gm. corn syrup
30 Gm. vegetable oil	3 Gm. agar
1 Gm. salt	3 teaspoons vanilla extract
1 Gm. cinnamon	250 cc. water
Pinch of nutmeg	

Mix all ingredients except agar. Cook until thick, add agar, mix in high speed blender and cool in refrigerator. For drink add additional 150 cc. of water.

2. Vegetable sauce (for one day)

30 Gm. vegetable oil	20 Gm. corn syrup
15 Gm. tapioca flour	2 Gm. salt
15 Gm. Essenamine	¼ teaspoon celery salt
¼ teaspoon chopped parsley leaves	¼ teaspoon onion salt
	75 cc. water

Mix thoroughly, and cook over medium flame until thick. Cool.

3. Fruit crisp (three servings for one day)

200 Gm. fruit	100 Gm. brown sugar
5 Gm. tapioca flour	15 Gm. Essenamine
2 Gm. salt	1 Gm. cinnamon
30 Gm. oil	Pinch of nutmeg
	Water if necessary

Mix until crumbly. Line a baking pan with some of fruit. Add mixture. Bake in a moderate oven until brown. Divide into three servings.

II. Diets for high Essenamine intake

A. Low residue diet plus 150 Gm. of Essenamine in 1,500 cc. of milk drink

1. Menu

Breakfast	Lunch	Dinner
Fruit	Egg or meat or cheese	Soup
Cereal or eggs	Potatoes	Cheese
Bread	Vegetable	Bread
	Bread	Canned fruit or ice cream

Drink is divided into six portions—three with meals and three between meals and bedtime.

2. Recipe for Essenamine milk drink

60 Gm. corn starch	4 teaspoons vanilla extract
150 Gm. Essenamine	½ teaspoon nutmeg
40 Gm. brown sugar	2 teaspoons cinnamon
100 Gm. corn syrup	750 cc. milk
1 egg	17.5 Gm. powdered malted milk
3 Gm. salt	150 Gm. chocolate syrup
	500 cc. water

Mix all ingredients except milk, egg and chocolate syrup. Cook until thick. Cool slightly, and add remaining ingredients. Blend at high speed for fifteen to twenty minutes. Serve chilled.

(Carbohydrate 276 Gm., protein 197 Gm., fat 47 Gm. and calories 2,315)

B. High Essenamine diet (160 Gm. of Essenamine)

1. Menu

Breakfast

Orange
Oatmeal (20 Gm. of Essenamine)
Muffin (10 Gm. of Essenamine)
Fruit pudding (10 Gm. of Essenamine)
Drink 250 cc. (16.67 Gm. of Essenamine)

Lunch

Meat loaf (10 Gm. of Essenamine)
Vegetable puree (10 Gm. of Essenamine)
Muffin (10 Gm. of Essenamine)
Pudding (10 Gm. of Essenamine)
Drink 250 cc. (16.67 Gm. of Essenamine)

Supper

Vegetable puree (10 Gm. of Essenamine)
Fruit pudding (10 Gm. of Essenamine)
Muffin (10 Gm. of Essenamine)
Drink 250 cc. (16.67 Gm. of Essenamine)

2 Recipes

(*a*) Drink

3 Gm. agar dissolved in 40 cc. boiling water	25 Gm. tapioca flour
50 Gm. Essenamine	15 Gm. vegetable oil
35 Gm. brown sugar	2 Gm. salt
1½ teaspoon vanilla	¼ teaspoon nutmeg
½ egg	720 cc. milk
	Water if needed

Prepare as for aforementioned drink.

(*b*) Muffins (three for one day)

30 Gm. Essenamine	⅓ teaspoon baking powder
10 Gm. flour	¼ teaspoon salt
7 Gm. sugar	½ teaspoon vanilla
1 egg	
75 cc. water	

Sift the dry constituents, add liquid and fold in the beaten white of egg. Bake in a moderate oven until done.

(*c*) Sauce for vegetable, soup or meat

	15 Gm. corn syrup
30 Gm. Essenamine	2 Gm. salt
5 Gm. oil	½ teaspoon onion, celery or parsley flakes
15 Gm. flour	200 cc. water

Mix all ingredients with water and cook over moderate flame until thick. Divide into three parts and use with vegetables, soup or meat.

(*d*) Sauce for fruit

40 Gm. Essenamine
80 Gm. corn syrup
20 Gm. corn starch
175 cc. water
1 teaspoon cinnamon
½ teaspoon vanilla
Pinch nutmeg

Mix all ingredients together, and cook over medium flame until thick. Add 250 or 300 Gm. of fruit puree. Makes three servings.

(*e*) Meat loaf

75 Gm. ground beef
5 Gm. onion
5 Gm. oil

Mix with one third of the recipe for vegetable sauce. Bake in casserole.

Mrs. Hazel Parks, dietitian for the study, prepared all diets and recipes. Miss Shandus Pincoffs was her assistant. Miss Millie E. Kalsem, chief executive dietitian of the Cook County Hospital, cooperated and gave advice at all stages of the study.

LOCALIZED PROXIMAL JEJUNITIS

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IN 1932, Crohn, Ginzburg and Oppenheimer [1] first described the clinicopathologic entity which was called "terminal ileitis." Since then, many instances of the same pathologic process in all parts of the ileum and jejunum have caused modification of the term to "regional enteritis." Of the numerous cases reported, however, in only a few has the disease been limited to the jejunum. Harris, Bell and Brunn [2] first described a case with the lesion wholly in the jejunum. Brown and Donald [3] included in their 178 cases of regional enteritis 5 instances of primary jejunal lesions. W. R. Johnson [4] reported a case with multiple diseased segments which were all confined to a few feet of jejunum and for which resection with end to side anastomosis was performed. H. N. Brewster [5] also described an instance of localized obstructing jejunitis in a small section of bowel treated by resection and anastomosis.

In the present report of a case, localized jejunitis, found at operation, involved approximately 10 inches (25 cm.) of jejunum but the upper limit was at the ligament of Treitz. On the basis of experience at the Mount Sinai Hospital, as reported by Garlock and Ginzburg,[6] which had demonstrated the effectiveness of simple ileocolostomy with exclusion but without resection in regional enteritis of the terminal portion of the ileum, the same principle was applied in the present case of enteritis localized to the jejunum.

From the Surgical Service, Mount Sinai Hospital.

1. Crohn, B. B.; Ginzburg, L., and Oppenheimer, G. D.: Regional Ileitis: Pathologic and Clinical Entity, J. A. M. A. **99**:1323 (Oct. 15) 1932.

2. Harris, F. I.; Bell, G. H., and Brunn, H.: Chronic Cicatrizing Enteritis: Regional Ileitis (Crohn) New Surgical Entity, Surg., Gynec. & Obst. **57**:637 (Nov.) 1933.

3. Brown, P. W., and Donald, C. J.: Prognosis of Regional Enteritis, Am. J. Digest. Dis. **9**:87 (March) 1942.

4. Johnson, W. R.: Chronic, Non-Specific Jejunitis with Unusual Features, Gastroenterology **1**:347 (April) 1943.

5. Brewster, H. N., cited by Crohn, B. B., in discussion on Johnson.[4]

6. Garlock, J. H., and Ginzburg, L.: Regional Ileitis, Ann. Surg. **116**:906 (Dec.) 1942.

Accordingly, the lesion was short circuited by transecting of the jejunum distal to the lower limits of the jejunitis and performing of a side to side duodenojejunostomy between the third portion of the duodenum and the jejunum, which had been severed distal to the lesion. The patient's postoperative course was uneventful, his symptoms disappeared and he has remained well in the three year interval since operation.

Roentgenogram showing the typical "string" sign confined to the proximal 10 inches of jejunum. The lesion is sharply demarcated.

REPORT OF A CASE

History.—A. N., a 30 year old white Jewish man, was admitted to the Mount Sinai Hospital on Oct. 25, 1943, with a three year history of intermittent, paraumbilical, dull and boring pain, occurring often, but not invariably, after eating and lasting from five minutes to a half-hour. There was no nausea, vomiting or change in bowel habit. Roentgenologic studies in the Army showed "some abnormality of the small intestinal pattern," but after a tentative diagnosis of nontropical sprue the patient was finally considered to be psychoneurotic and was discharged from the service.

Following discharge, the pains increased in intensity and frequency and were often associated with nausea and vomiting. Appetite declined, and the patient lost 30 pounds (13 Kg.). Both appetite and weight were partially regained on a regimen which included parenteral administration of vitamin B complex and insulin. Radiation therapy to the abdomen seemed to lessen the degree and frequency of pain. However, the symptoms continued severely enough to prevent the patient from working.

Finally, careful roentgenologic studies of the small bowel showed a localized area of constriction in the jejunum, starting at the duodenojejunal junction and extending for about 10 inches (fig. 1).

Examination.—The patient was thin and showed evidence of loss of weight but was not dehydrated. The temperature was 99.6 F. and the pulse rate 84. There were no other significant physical findings except slight tenderness in the midline of the upper part of the abdomen, just above the umbilicus. No masses were palpable.

Laboratory Data.—The hemoglobin content (Sahli) was 83 per cent, red blood cell count 4,800,000 and white blood cell count 5,600, with segmented polymorphonuclears 55 per cent, nonsegmented polymorphonuclears 20 per cent, lymphocytes 21 per cent, monocytes 3 per cent and eosinophils 1 per cent.

The urine gave an alkaline reaction; specific gravity was 1.010; examinations for albumin and sugar and microscopic examination gave normal results.

Operation (Dr. John H. Garlock).—On Oct. 26, 1943, with the patient under ethylene-ether anesthesia, a midrectus muscle-splitting incision was made on the right side. The jejunum, beginning at the ligament of Treitz and extending for a distance of 10 inches, was decidedly reddened, and the wall was thickened. The mesentery of the inflamed segment of jejunum was edematous and contained several large lymph nodes. The area of involvement of the intestine ended sharply. The remainder of the entire small intestine was carefully inspected and found to be normal.

Six inches (15 cm.) distal to the lower border of the jejunitis, the jejunum was transected and each end inverted with three layers of silk. The distal limb was brought up beneath the transverse colon to the third portion of the duodenum. A side to side duodenojejunostomy was made, fine chromic surgical gut being used on the mucosal layers and fine silk for the serosal surfaces. The wound was closed with buried, interrupted figure of eight, steel alloy wire sutures. The skin was approximated with clips.

Course.—The postoperative course was uneventful except for a gradual rise in temperature, reaching 102 F. on the third day. The temperature was normal by the seventh day, where it remained until the patient was discharged, thirteen days after operation. The bowels were moving normally every other day at the time the patient left the hospital.

Follow-up.—The patient has had no recurrence of intestinal symptoms and has gained weight. At the last visit his general condition was excellent and his abdomen nontender.

SUMMARY

This is the first reported instance of localized jejunitis treated by a short-circuiting procedure without resection.

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